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RELATION OF THE CEREBRAL CORTEX TO THE GRASP REFLEX AND TO POSTURAL AND RIGHTING REFLEXES

I. BIEBER, M.D.*
NEW YORK
AND
J. F. FULTON, M.D.
NEW HAVEN, CONN.

It has long been recognized that many of the postural reflexes described by Magnus cannot be demonstrated when the cerebral cortex is intact. The region of the cortex normally concerned in suppressing these reactions, however, has never been determined. Fulton and Keller [1] could not elicit the postural neck reflexes in monkeys and chimpanzees from which one or both motor areas (area 4 of Brodmann) had been removed, and it has since been found in this laboratory that the thalamic righting reflexes are not obtainable in such preparations. Evidently, therefore, some other cortical area or areas are also concerned in suppressing these reactions.

In a study of cortical pareses in monkeys [2] it was found that integrity of a portion of one premotor area (area 6a of Vogt) in animals from

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From the Laboratory of Physiology, the Yale University School of Medicine.

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1. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

2. (*a*) Fulton, J. F., and Kennard, Margaret A.: A Study of Flaccid and Spastic Paralyses Produced by Lesions of the Cerebral Cortex in Primates, A. Research Nerv. & Ment. Dis., Proc. **13**:158-210, 1934. (*b*) Fulton, J. F.: Paralyses of Cortical Origin: A Physiological Analysis of Flaccid and Spastic States in Monkeys and Chimpanzees, Proc. California Acad. Med., 1933-1934, pp. 1-20; (*c*) Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area: A Physiological Analysis, Arch. Neurol. & Psychiat. **31**:221-235 (Feb.) 1934.

which both motor areas had been ablated made possible the execution of fairly well coordinated volitional movements in all four extremities, greater dexterity being seen in the extremities opposite the intact premotor region. However, when the motor and premotor areas were completely removed from both sides in adult monkeys, volitional movements became virtually abolished; i. e., such animals were quite unable to stand, walk or feed themselves, even after four months. In addition our present investigation has revealed that animals prepared in this manner exhibit the body righting reflexes, the labyrinthine reflexes of Magnus and de Kleyn [3] and occasionally the neck reflexes; as long as they lived, moreover, they showed in a striking manner the phenomenon of the grasp reflex. In addition, the animals exhibited a characteristic attitude or "postural pattern," which changed in accurately predictable fashion with alterations of the animal's position in space. When the animal was lying on one side with head reclining in the lateral position,

Fig. 1 (corpus callosum series, no. 1).—The thalamic postural pattern in an adult macaque four months after removal of the left motor and premotor areas, and two days after removal of the right cerebral hemisphere. Note the extended posture of the underlying extremities and the strongly flexed posture of the uppermost extremities. The animal showed the neck and labyrinthine reflexes of Magnus and de Kleyn and the body righting reflexes. It was killed on June 19, 1933, thirty-three days after ablation of the hemisphere.

the underlying upper and lower extremities were extended and rigid but failed to show reflex grasping, while the uppermost limbs were strongly flexed and exhibited reflex grasping on gentlest contact with the palmar or plantar surface (fig. 1). When the animal was turned over the postural pattern was reversed.

This postural reflex pattern had been described in 1922 by Magnus in thalamic monkeys.[4] He pointed out that in the lateral position such preparations maintained an attitude consisting of extension of the under-

3. Magnus, R.: Körperstellung: Monographien aus dem Gesamtgebiet der Physiologie der Pflanzen und der Tiere, Berlin, Julius Springer, 1924.

4. Magnus, R.: Körperstellung und Labyrinthreflexe beim Affen, Arch. f. d. ges. Physiol. **193**:396-448, 1922.

lying limbs and flexion of the uppermost limbs and that the posture was unchanged after bilateral labyrinthectomy and was essentially uninfluenced by torsion or bending of the neck. Magnus traced the afferent source of the pattern to asymmetrical stimulation of the trunk and the lateral surface of the thigh; i. e., the postural reactions fall into the category of "the body righting reflexes acting on the body." He made no attempt, however, to analyze the possible relation of the postural status of thalamic monkeys to the motor projection systems of the cortex or striatum, and only passing mention was made of the presence of a strong grasp reflex. Magnus did not associate this with the forced grasping phenomenon of the clinician, nor did he observe its relation to the position of the animal in space. The pattern of response just described was not present in decerebrate monkeys—a fact we have also observed in unpublished studies. It must therefore depend on the integrity of some centers above the pons. For purposes of exposition we propose to call this attitude and the predictable changes which it undergoes with alteration of the body position "the thalamic reflex pattern."

It may thus be regarded as highly significant that the pattern of response in thalamic preparations appears to be identical with that of adult monkeys after bilateral ablation of motor and premotor areas, and the fact that the grasp reflex is so intimately associated with the righting reflexes raises the question whether the grasp may not also be a part of these basic postural mechanisms. The observations now recorded help to elucidate this relationship.

METHODS

The details of the operative technic employed have been described elsewhere.[1] The majority of operations were carried out with the animal under sodium amytal anesthesia (given intraperitoneally). Extirpations were generally made at successive operations, and secondary procedures were ordinarily not undertaken until a virtually stationary [5] neurologic status had been arrived at after the previous operation. In making extirpations, precautions were taken to remove all cortical tissue in the depths of the sulci (e. g., the sulcus cinguli) forming the anatomic

5. By "virtually stationary" we mean that an increment of improvement was not observable from day to day. Such a status is generally established in macaques within about three to four weeks after a regional ablation of the motor cortex; but the more one observes adult monkeys after cortical lesions the more obvious it becomes that movements as such increase more or less steadily in complexity for several years after a motor lesion. A baboon was recently killed over five years after ablation of the hand areas (baboon no. 2). This animal had shown improvement in finger movements over a period of three years, but no clearcut signs of increased dexterity were observed during the last two years of its life. Similar observations were made in a chimpanzee ("Mussai") which exhibited steady increase in manual dexterity for a period of three years after lesions of premotor and motor hand areas.

boundaries of the area in question. Microscopic sections were made of blocks of tissue removed, and sections of the cortex obtained at autopsy were also studied.

Various combinations of lesions were secured, and in one animal the extirpations of the motor and premotor areas of both hemispheres were carried out in one stage. The reflex manifestations were studied by ordinary clinical methods and recorded by means of still photographs, drawings and motion pictures. To facilitate description the Brodmann-Vogt numerical designation for the several cyto-architectural fields will be employed: Thus, area 4a refers to the area giganto-pyramidalis controlling the leg; area 4b, to the corresponding area for the arm, and area 6a (upper part), to the "premotor area." In describing the prehension reflexes of the digits, a distinction is made between clinical "forced grasping," which is fickle and subject to unpredictable cortical influences, and the "grasp reflex," which is predictable, varies with the animal's position in space and is entirely subcortical in integration.[2c] It is clear, however, that the grasp reflex is the basic reaction responsible for forced grasping; but when, as in clinical cases of "forced grasping," the pyramidal tracts are intact, these involuntary prehension phenomena have temporal and other characteristics of intensity, fluctuation, etc., that distinguish them from the stereotyped grasp reflex of the thalamic preparation.

EXPERIMENTS AND OBSERVATIONS

THE THALAMIC REFLEX PATTERN

The conclusions arrived at in this paper are based on a group of fifteen experiments made in 1932 and 1933, from which the following abbreviated protocols have been selected as illustrations; confirmatory evidence has been obtained from many similar preparations which have subsequently been studied for other purposes (e. g., the influence of cortical lesions on the basal metabolic rate[6]).

EXPERIMENT 1 (premotor series, no. 4).—*Bilateral removal of motor and premotor areas at successive operations; profound voluntary paralysis for thirty-five days with presence of postural and righting reflexes; inadequate progression movements regained; termination of experiment after five months; small area of left premotor cortex intact.*

The subject of the experiment was a young female baboon (Papio cynocephalus) weighing 4,250 Gm. The animal was healthy, and movements were normal. Its history, with reference to motor paralysis, has been described by Fulton and Kennard[2] (experiment 5).

First Operation (July 13, 1932).—Removal of left motor and premotor areas. The left motor and premotor regions were removed in one block (fig. 2). On the first day following the operation, the animal exhibited characteristic right hemiplegia, with weak hip flexion remaining as the sole spontaneous movement. The return of power was rapid, the increment of daily improvement progressively decreasing until a permanent status was arrived at in about one month. Movements at the proximal joints reappeared earlier and more completely than those at the more distal joints. After a month residual weakness of the right extremities, especially of the fingers, still existed, and the right forelimb often failed to support the weight of the animal in climbing. For feeding the left hand was employed exclusively.

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6. Rakieten, N.: Changes in Heat Production After Removal of Motor and Premotor Areas in Monkeys, Am. J. Physiol. **114**:661-666 (Feb.) 1936.

The first evidence of a grasp reflex was observed in the right upper extremity on the sixth postoperative day. From the eighth to the sixteenth day it was well marked and elicited with ease. After the sixteenth day the reflex began to disappear, and on the twenty-second day after operation it was completely gone. The grasp reflex did not appear in the right lower extremity.

Second Operation (October 24).—Removal of right motor and premotor areas. On the day after the operation, the animal was incapable of righting itself or of maintaining the standing position, and it manifested the characteristic reflex pattern already referred to and described in detail later (fig. 3). The return of power was extremely slow, especially to the hindlimbs. The animal was unable to walk until the thirty-fifth day after operation, and then only with much insecurity and awkwardness. Five months after the second operation the gait was still bizarre,

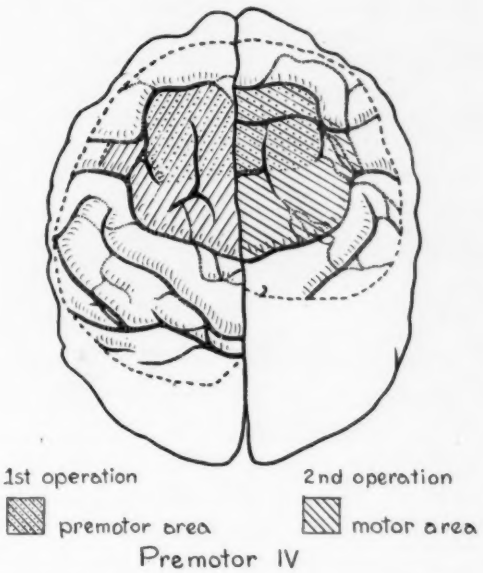

Fig. 2 (experiment 1).—Diagram showing the motor and premotor areas of the baboon.

the animal being scarcely able to progress, but the standing position was maintained without much difficulty.

Third Operation (March 21, 1933).—Section of posterior roots. Section of the right posterior nerve roots from the third cervical to the second thoracic level was followed by slight diminution of the grasp reflex in the right hand (see discussion in a succeeding portion of the text). The animal was killed on March 27.

Autopsy.—Sections of the hemisphere showed that all of both motor areas had been removed but that the anterior part (about one tenth as estimated by surface area) of the premotor region in the left hemisphere was still intact. Marchi sections of the brain stem and the cord revealed the usual picture of degeneration of the pyramidal tracts, with early ascending degeneration from the posterior root section. The peripheral nerves in the right hindlimb also showed degeneration. (The animal lay on that side.)

In this experiment the thalamic postural pattern developed immediately after the motor and premotor areas had been removed from the second hemisphere, but some motor recovery occurred, owing in part to incompleteness of the operation. In the next experiment the areas were removed in four stages, and the thalamic pattern and the Magnus righting reflexes failed to appear until the final motor area had been removed. Similar results have been obtained when the final area was the premotor.

EXPERIMENT 2 (premotor series, no. 8).—*Successive removal of motor and premotor areas at four operations; complete voluntary paralysis with postural and righting reflexes; death from meningitis five days after last operation.*

The experiment was carried out on a young male capuchin monkey (Cebus fatuellus) weighing 1,900 Gm., observations on which Kennard and Fulton [2] (experiment 4) have discussed in connection with cortical paralysis.

Fig. 3 (experiment 1).—The thalamic reflex pattern in the baboon ten days after bilateral removal of the motor and premotor areas. The face and neck representation remained intact in this animal, which accounts for the position of the head. Note the extension of the underlying extremities and the flexion of the uppermost extremities.

First Operation (Sept. 27, 1932).—Ablation of left motor area. The ablation included only the representation of the extremities, the face area being spared. The day after the operation the animal showed right hemiplegia, but there was rapid reappearance of spontaneous activity in the affected limbs, movements being most pronounced in the proximal joints. The grasp reflex was not present.

Second Operation (October 3).—Removal of left premotor area. The premotor area was removed, and microscopic sections through the block failed to disclose any Betz cells. Immediately after the operation, however, the right extremities exhibited a loss of the power they had regained, and recovery of power proceeded much more slowly than after destruction of area 4 alone. A weak grasp reflex was observed in the right upper extremity on the third day. It did not become well marked and disappeared after several days.

Third Operation (October 22).—Removal of right premotor area. This block of tissue also proved to be without Betz cells. Spontaneous movements of the right extremities were not materially altered by the operation, but the left lower

extremity exhibited slight weakness. The left arm, however, showed no obvious loss of force, but the left extremities were awkward and lacked the precision of movement manifested by normal animals. Although at this stage only the right motor area remained of the cortical motor representation, the reflex pattern described later did not appear, and the Magnus and de Kleyn reflexes could not be demonstrated.

In the left upper extremity the grasp reflex was well marked on the morning after operation and remained so for one week. On the fourth day a weak grasp reflex was obtained from the right forelimb. This increased in intensity and in ease of elicitation until, at the end of this interoperative interval, it was as pronounced as at any period in the experiment.

Fourth Operation (November 3).—Removal of right motor area. The right hemisphere was exposed and the motor area, which was normal in appearance, was stimulated and then removed. Sections of the block contained Betz cells almost to the anterior margins. Immediately after recovery from the anesthetic, the animal presented the reflex pattern described later, with the grasp reflex present in all extremities and the postural and reflex pattern of Magnus. Meningitis developed on the fourth day, and the animal died on the fifth. There had been no recovery of voluntary power.

Autopsy.—Gross examination showed that the cortical areas 6a and 4a and b had been satisfactorily removed on both sides, but microscopic studies of the cortex were not made. The meningitis was localized in the temporal region of the left hemisphere.

The experiment illustrates clearly the bilateral character of the influence exerted by the cortex over the subcortical postural mechanism: It is undoubtedly significant that grasping appeared to be influenced to the same extent as the postural reactions by the remaining cortical area.

The next experiment was similar to this except that the sequence of extirpation was altered. The animal survived for forty-five days in the thalamic state and was therefore available for detailed examination.

EXPERIMENT 3 (premotor series, no. 11).—*Successive removal of motor and premotor areas from both hemispheres; appearance of thalamic pattern after fourth operation; no return of voluntary power during forty-eight days' survival.*

The subject of the experiment was an adult male monkey (Macaca mulatta) weighing 4,300 Gm.

First Operation (Nov. 26, 1932).—Removal of left premotor area. This lesion, which involved only the left premotor region, did not seriously impair spontaneous activity or motor power of the right extremities. Early in the postoperative period there were some weakness and lack of precision in the use of the limbs, noticeable only when the animal jumped or became fatigued. The grasp reflex was first observed in the right forelimb on the third day, reaching maximal intensity on the fifth. After the ninth day the reflex began to diminish, and it had completely disappeared on the eighteenth day.

Second Operation (Jan. 4, 1933).—Removal of right premotor area. On the first day following operation the animal walked about the cage in a fairly normal fashion. Both hands, however, were abnormally everted, being maintained almost at right angles with the longitudinal axis of the body. Passive manipulation of

the extremities revealed increased resistance of the right limbs both to flexion and to extension. A poorly sustained grasp reflex was elicited in all four extremities. Both the resistance to passive manipulation and the grasp reflex in the right limbs reached maximal intensity on the third day after operation and then began to decline concurrently. On the twenty-third day after the second operation there was no detectable difference in the resistance to passive movement of the upper extremities. The resistance to passive flexion, however, was definitely greater in the right lower limb than in the left. The grasp reflex could not be elicited.

Third Operation (January 27).—Removal of left motor area. All precentral tissue to the depths of the central sulcus was removed at the third operation. The block proved to include area 4 tissue almost exclusively. The face area was spared. The resulting weakness on the right side, profound during the first five days, gradually disappeared, and after ten days a substantial degree of spontaneous activity was observed even in the more distal joints. At this time, despite the co-existing deficit of both premotor areas, moderately coordinated progression was possible.

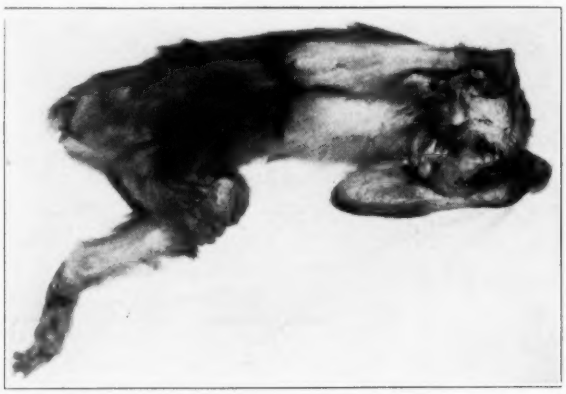

Fig. 4 (experiment 3).—Resting posture of a macaque on Feb. 20, 1933, three weeks after the final operation. Grasping was so vigorous in the upperlying extremities that the animal clutched its underlying leg and scalp with the overlying extremities. In this animal the underlying upper extremity was sometimes flexed, as shown in the photograph.

Grasp Reflex.—A weak involuntary grasp reflex was occasionally obtained from the right forelimb. No similar response was elicited from the other extremities, and there was no trace at any time after the second operation of the thalamic pattern or of the reflexes of Magnus and de Kleyn.

Fourth Operation (February 1).—Removal of right motor area. The block of precentral tissue removed at the fourth operation contained area 4 tissue and a small amount of tissue left from the second operation. The face area was spared. After recovery from the anesthetic, the animal lay on its side, totally incapacitated, and exhibited the postural status characteristic of the thalamic monkey (fig. 4). Not until the twenty-first postoperative day was the animal able to right itself from the lateral position, and even then only the fore half of the limb was brought to the prone posture. Although the animal lived for forty-eight days after the fourth operation, it did not regain the ability to stand or to feed itself.

Grasp Reflex.—This was present in the four extremities until the animal's death. The relation of the grasp reflex to the other postural reflexes observed in this animal is described later in the text.

Microscopic Study.—Sections of the internal capsules, brain stem and cord stained by the Marchi and Spielmeyer technics showed extensive degeneration in both pyramids at all levels of the brain and cord; cell stains of sections of the hemispheres which were later studied for us by Dr. Paul C. Bucy failed to disclose any motor or premotor tissue. Marchi sections revealed early degeneration in the peripheral (peroneal and popliteal) nerves of the hind extremities.

This experiment substantiates the preceding observations and indicates that even after seven weeks recovery of motor power is minimal and that the grasp reflex and the postural reflex pattern of Magnus continue without diminution of intensity.

Observations on the next animal are included to illustrate the striking character of the thalamic attitudes seen post mortem.

EXPERIMENT 4 (area 6 series, no. 1).—*Successive removal of left motor and premotor areas (two stages) and of right motor and premotor areas; seven days' survival; thalamic posture, no return of volitional activity.*

The subject of this experiment was a mature male rhesus (Macaca mulatta) weighing 4,800 Gm.

First Operation (Jan. 5, 1933).—Removal of left motor area. The course following this procedure was, in the main, identical with that previously described for a lesion of the motor area. After three weeks the flaccid hemiplegia, present immediately after operation, had improved sufficiently to permit the animal to use its right limbs somewhat awkwardly in walking and climbing. The grasp reflex did not appear during the postoperative interval, and other postural reflexes could not be demonstrated.

Second Operation (January 26).—Removal of left premotor area. After this extirpation the hemiplegic symptoms became markedly exaggerated, and the extremity exhibited spastic rigidity. After two weeks, however, the animal was able to climb about its cage readily, the right hindlimb being employed to better advantage than the forelimb. The rigidity gradually diminished. The grasp reflex was observed in the right upper extremity during the first few days of the postoperative period.

Third Operation (February 9).—Removal of right motor and premotor areas. The thalamic postural status appeared eight hours after operation. The grasp reflex was present in the four limbs; the tonic neck reflexes of Magnus and de Kleyn were also observed. At the time of the animal's death (from acute intussusception), on the seventh postoperative day, there was no spontaneous activity in any limb. Full details concerning this animal have been reported in another connection (Bucy and Fulton,[7] experiment 8). The animal lay on its right side, and when it died it went into rigor mortis in the thalamic position, as is illustrated in the photograph taken post mortem (fig. 5).

The following experiment was designed to disclose how soon the thalamic posture might appear after removal of the excitable area from both hemispheres.

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7. Bucy, P. C., and Fulton, J. F.: Ipsilateral Representation in the Motor and Premotor Cortex of Monkeys, Brain **56**:318-342 (Sept.) 1933.

EXPERIMENT 5 (intussusception series, no 5).—*Acute experiment involving simultaneous ablation of motor and premotor regions from the two hemispheres; immediate appearance of thalamic attitude with the grasp reflex in all extremities.*

The subject of the experiment was a mature rhesus (Macaca mulatta) weighing 4,750 Gm. in which both hemispheres had been exposed for purposes of stimulation. When these observations had been made, the motor and premotor areas were removed from each hemisphere (March 16, 1933). About ten minutes after removal of the excitable areas from each hemisphere, the animal had recovered from the ether anesthesia. At this time the thalamic postural status was already evident. The grasp reflex was present in all extremities, bearing its usual relation to the characteristic reflex pattern. A laparotomy was then performed under light ether narcosis and the animal permitted to recover. With the monkey in the supine position, the viscera were displaced from side to side. These maneuvers did not influence the posture of the animal.

Fig. 5 (experiment 4).—The thalamic reflex posture as seen in rigor mortis, shortly after the death of the animal.

INFLUENCE OF CUTANEOUS ANESTHESIA AND SECTION OF POSTERIOR ROOTS ON GRASP REFLEX AND THALAMIC REFLEX PATTERN

The fact that in bilateral motor-premotor preparations the grasp reflex is a constant phenomenon affords an opportunity of analyzing the mechanism of the grasp itself. Recent clinical studies [8] have indicated that exteroceptive and proprioceptive stimuli both play a part in evoking the grasp, and it has been possible in these thalamic reflex preparations to assess the importance of each form of stimulation in turn.

Exteroceptive Innervation.—Since the cutaneous receptive field can be debarred by the use of local anesthetics, it is possible to separate the proprioceptive from the exteroceptive innervation. The cutaneous reflexogenous zone is important in relation to the grasp reflex, since some clinicians have maintained that forced grasping depends largely,

8. Walshe, F. M. R., and Robertson, E. Graeme: Observations upon the Form and Nature of the "Grasping Movements" and "Tonic Innervation" Seen in Certain Cases of Lesions of the Frontal Lobe, Brain **56**:40-70 (March) 1933.

if not solely, on cutaneous stimulation.[9] In experiment 3 after the fourth operation (and in two other bilateral preparations of this type) complete anesthesia of the hand was obtained by local infiltration of a cuff of skin above the wrist with a 1.5 per cent solution of procaine hydrochloride. When conspicuous anesthesia had been produced, the grasp reflex could still be elicited by gentle contact with the digits of the upperlying forelimb in such a manner as slightly to stretch their tendons; it could be obtained also by placing the shoulder muscles under tension. This maneuver involves extension of the elbow and shoulder joints, with attendant stretching of the flexor muscles of the elbow and shoulder. The grasping produced in this manner did not differ from that elicited by so-called cutaneous stimulation in the unanesthetized monkey.[10]

If the grasp reflex is considered as part of a postural response of the limb, its production by stretching of the flexor muscles is less surprising.[11] Rademaker [12] showed the *Aufziehreaktion* in dogs and cats

9. Schuster, P.: (*a*) Zwangsgreifen und Nachgreifen, zwei posthemiplegische Bewegungsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:586-609, 1923; (*b*) Autoptische Befunde bei Zwangsgreifen und Nachgreifen, ibid. **108**:715-733, 1927.

10. Careful study of the grasp reflex in these preparations indicates that very gentle contact with the skin of the digits is sufficient to evoke the response, but such contact inevitably gives a slight stretch to the digital tendons. Stroking the skin of the palm or fingers with mouse or camel hairs or with light cotton does not ordinarily evoke a grasp, even though of an intensity easily "felt" on corresponding areas of human skin. The observation on anesthesia previously mentioned in the text clearly indicates that the cutaneous component of the reflexogenous zone is unessential for the grasp; whether the exteroceptors contribute materially to the grasp reflex in normal circumstances must be left an open question, but it seems highly improbable that they exert a primary influence on the reaction in animals.

11. Walshe and Robertson [8] were the first to stress the fact that the grasp reflex is essentially proprioceptive in origin and that it forms a part of a more generalized postural reflex of the extremity. To make their excellent observations intelligible to the general reader it should be noted that they insist on a rather special terminology which has not yet had wide acceptance; i. e., "forced grasping" they describe as "grasping movements" which are subject, as all agree, to secondary integrations of cortical origin; to the "grasp reflex" itself—a purely subcortical affair—they give the term "tonic innervation." We heartily sympathize with these distinguished writers in their desire to emphasize that the grasp reflex is an integral part of an important postural mechanism (this indeed is our own conclusion), but since the reflex is one which can be studied separately, we believe that it merits independent designation. "Grasp reflex" seems wholly appropriate as a descriptive term. To refer to such a specific reaction by a generalized term is equivalent to designating Rademaker's "positive supporting reaction" also as "tonic innervation," or Babinski's sign as the "flexor reflex."

12. Rademaker, G. G. J.: Das Stehen, Berlin, Julius Springer, 1931.

to be dependent on stretching of the elbow and shoulder flexors. The reaction consists of flexion of the elbow and shoulder joints when an animal is raised from a surface by its forepaws. In cats a modified form of grasp reflex, consisting of protrusion of the claws, accompanies the *Aufziehreaktion.*

This leads us to consider the proprioceptive component of the grasp reflex, which, unfortunately, cannot be separated from the exteroceptive component; however, by section of the posterior nerve roots both the proprioceptive and the exteroceptive elements can be simultaneously destroyed.

Section of Posterior Roots.—For purposes of analysis, the posterior root innervation of one upper extremity was interrupted both before and after production of the thalamic reflex pattern. In the following experiment the right distal dermatomes of the forelimb were first deafferented, cortical lesions being made subsequently to establish the thalamic reflex pattern. The deafferented extremity then showed forced grasping only when the more proximal muscles of the limb were stretched. When the animal was in the left lateral position and the fore half of the left side of the body was elevated from the table, the right forelimb became flexed, and a moderately firm grasp enduring about thirty seconds was elicited. The grasp reflex thus possesses a wide proprioceptive reflexogenous zone, with the proprioceptors of the digits as the primary focus for the reaction. The tendons of the elbow and shoulder muscles, especially the flexors of these joints, are also highly effective zones of stimulation, as the following experiments indicate.

EXPERIMENT 6 (premotor series, no. 15).—*Thalamic reflex pattern induced by cortical ablation after deafferentation of right upper extremity (from third cervical to first thoracic level); grasp reflex present in left but absent from right upper extremity except when shoulder was placed under stretch; thalamic posture assumed in all extremities; thirty-seven days' survival.*

The subject of the experiment was a female monkey (Macaca mulatta) weighing 3,300 Gm.

First Operation (March 25, 1933).—Removal of left motor and premotor areas. Areas 4a and b and 6a were ablated from the left hemisphere. On the first postoperative day the disability of the right extremities was profound; gradual improvement occurred, the recovery running a course similar to that already described after corresponding lesions in other macaques. A poorly sustained grasp reflex was present in the right forelimb on the seventh day. The response was absent in the other extremities.

Second Operation (April 1).—Section of right posterior roots from first cervical to first thoracic level. After extradural deafferentation of all posterior nerve roots from the third cervical to the first thoracic segment, the right upper extremity was completely flaccid and anesthetic, and the grasp reflex could no longer be elicited from this limb by ordinary means.

Third Operation (April 11).—Ablation of right motor and premotor areas. After removal of areas 4a and b and 6a from the right hemisphere the thalamic

reflex pattern became completely established within a few hours. The right upper extremity, although deafferented, became flexed when the animal was placed in the left lateral position and extended when the body was turned to the right lateral posture. The grasp reflex could be elicited from all four extremities. In the deafferented forelimb, however, the reflex could not be obtained by contact with the palmar skin, but was elicited only by raising the limb until the rostral half of the body was elevated from the underlying surface. Further observation indicated that the grasp was obtained in the deafferented limb only when the shoulder muscles were placed slightly under stretch.

Tonic Neck Reflexes.—This animal manifested a series of responses to torsion of the neck not seen so clearly in the other experiments. In the prone position rotation of the head with the chin to the right produced extension of the left extremities and flexion of the right. With the chin to the left the posture was reversed. In the supine position, however, rotation of the head resulted in postural changes conforming to those described by Magnus and de Kleyn, i. e., extension

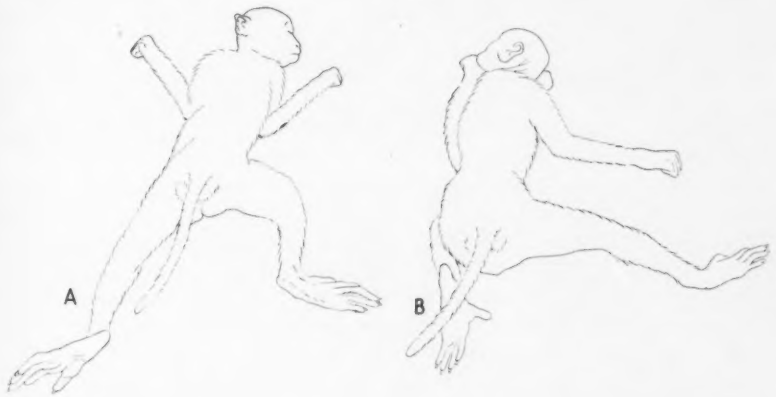

Fig. 6 (experiment 6).—Drawings showing the effect of turning of the head on the posture of the extremities when the animal was in the prone position. When it was in the supine position turning of the head caused extension of the extremity on the side toward which the head was turned and flexion on the opposite side, i. e., the conventional pattern of Magnus and de Kleyn.

of the *Kieferbein* extremities and flexion of the others. These postural reactions were repeatedly observed between April 13 and May 6 and were photographed and sketched (fig. 6*A* and *B*); after May 6 and until the animal was killed, on May 18, the Magnus and de Kleyn reaction became increasingly difficult to evoke. At the time of its death, on the thirty-seventh day following the last operation, the animal was still unable to stand and exhibited no volitional movement except in the head and neck muscles.

Autopsy.—The animal died of an acute gastric hemorrhage, and at autopsy several foci of recent ulceration in the mucosa of the lesser curvature of the stomach were observed by Dr. J. W. Watts. Section of the blocks of motor-premotor tissue removed at operation had indicated that the lesions were virtually complete. The entire brain was fixed in Müller's fluid, and Marchi sections were taken through the corpus callosum, internal capsule, pons, medulla and

cervical and lumbar portions of the cord. Both pyramids were degenerated, evidently in their entirety, and there were heavy ascending degeneration from the posterior root section (fig. 7*A*) and slight descending degeneration from the same source as low as the fourth lumbar level (fig. 7*B*).

In this experiment both the exteroceptive and the proprioceptive sensory fields were destroyed simultaneously, and so long as the shoulder and back muscles were not placed on stretch the grasp reflex was abolished; it is significant, however, that deafferentation did not abolish the reflex pattern.

Four experiments similar to this have been performed in which the posterior root section was more extensive, and in one other instance it was carried out prior to establishment of the thalamic reflex pattern. Thus, in the following experiments the posterior roots on the right side were severed from the third cervical to the eighth thoracic level and the motor and premotor regions removed from both hemispheres shortly thereafter.

EXPERIMENT 7 (premotor series, no. 22).—*Section of right posterior roots from third cervical to sixth thoracic level; thalamic reflex pattern established two weeks later in all four extremities by cortical ablation; grasp reflex greatly diminished in right upper extremity; two weeks' survival.*

The subject of this experiment was a large male macaque (Macaca mulatta), in excellent physical condition.

First Operation (Oct. 24, 1933).—Section of right posterior nerve roots from third cervical to eighth thoracic level. After the extensive deafferentation of the right upper extremity, the animal exhibited signs of complete sensory paralysis of the arm and hand, with evident ataxia of movement. The anesthesia continued without change as long as the animal lived.

Subsequent Operation.—On November 2 the left motor and premotor areas were completely ablated, after which the grasp reflex failed to develop in the right upper extremity. On November 6 the right motor and premotor areas also were removed. Immediately afterward the thalamic reflex pattern was established, all four extremities participating; i. e., the deafferented limb became extended when the animal was lying on its right side, with the right limb underneath, and flexed when the body was placed in the left lateral position. The grasp reflex, however, was sluggish, there being no response when the right palm was touched (with the animal in the left lateral position); only when the upper extremity was placed under considerable stretch did a grasping response occur, indicating that the body and some shoulder muscles innervated below the eighth thoracic level can evoke the grasp. Grasping, however, could also be induced in the right arm when the animal as a whole was moved rapidly through space. The animal was killed on November 18, because of having damaged the scalp by excessive grasping.

Autopsy.—The animal was in good health, and meningitis had not set in. Sample Nissl sections of the cortex extending from the postcentral to the frontal region (area 9) of both hemispheres indicated that areas 4a and b and 6a had been removed in their entirety. Marchi preparations of the cord showed strong ascending degeneration from the posterior root section and descending degeneration in the anterolateral and ventral columns. The picture was in every respect similar

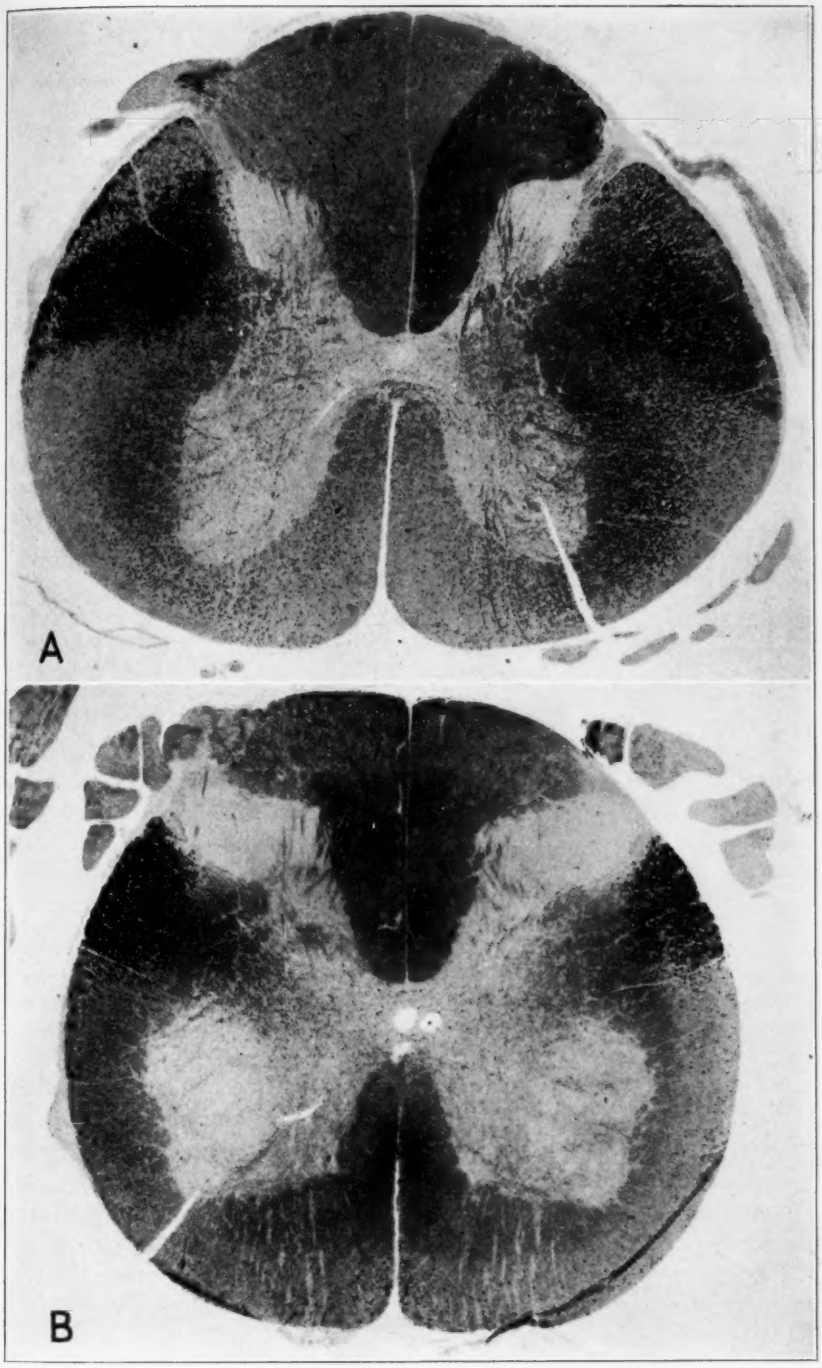

Fig. 7 (experiment 6).—Untouched Marchi sections of the spinal cord, (*A*) from the second cervical level, showing ascending degeneration in the right posterior column and descending degeneration in both pyramidal areas, and (*B*) from the first sacral level, contrasting heavy degeneration in both pyramidal areas and some descending degeneration in both pyramidal areas and some descending degeneration in both ventral columns.

to that shown in figure 7 *A* and *B*, in the preceding experiment. The posterior roots on the right side had been sectioned from the third cervical to the eighth thoracic level.

GENERAL DESCRIPTION OF POSTURAL REFLEXES PRESENT AFTER BILATERAL ABLATION OF MOTOR AND PREMOTOR AREAS

RIGHTING REFLEX AND THALAMIC REFLEX PATTERN

The close similarity of the thalamic reflex patterns in all the animals studied makes a general description applicable to each.

Thalamic Reflex Pattern.—When a bilateral motor-premotor animal is placed in the left lateral position, strong flexion occurs in the right extremities and extension in the left (figs. 1 and 8; see also experiment 4). The entire picture is reversed when the animal is placed in the right lateral position, with the left limbs in flexion and the right in extension. The extension of the underlying forelimb tended, several weeks after the final operation, to give way to semiflexion (fig. 4). Application of pressure to the uppermost side (*Brettversuch* of Magnus) diminished the degree of extension of the underlying limbs as well as the extent of resting flexion of the uppermost extremities, thus tending to make the two sides symmetrical. In animals with the face areas intact spontaneous variations in the position of the head, in relation both to space and to the trunk, did not materially alter the attitude, so long as the animal remained in the lateral position. The neck and

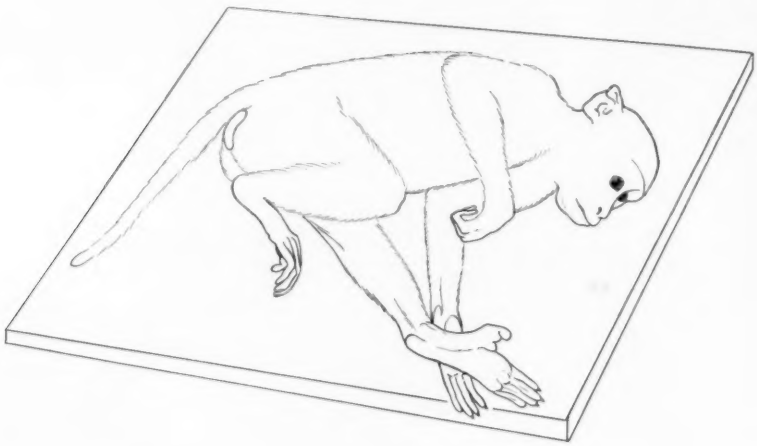

Fig. 8.—Diagram from a photograph of a bilateral motor-premotor preparation, showing the thalamic reflex pattern.

labyrinthine reflexes, although seen in some animals shortly after operation (experiment 6), were usually not conspicuous in these experiments (see a succeeding section). Exclusion of visual stimuli by blindfolding in no way affected the reflex posture.

The thalamic reflex pattern appears almost immediately after complete destruction of both the motor and the premotor areas. In experiment 5, in which this was performed at one operation, with the animal under ether anesthesia, the pattern was typical at the conclusion of the procedure. If but one motor area was retained (experiment 2)—or, more striking, if but one premotor area remained—it failed to appear. Once having set in, it tended to remain, with only minor variations, as long as any of the animals were studied. In experiment 1, five months after the final operation, extension of the underlying extremities and strong flexion of the uppermost extremities still occurred when the animal was placed in the lateral position.

The possibility of visceral stimuli arising in the omenta and visceral ligaments was also investigated. In experiment 5, after bilateral motor-premotor extirpation, the abdomen was opened, with the monkey under light ether narcosis. With the animal in the supine position, the viscera were shifted from side to side, but such maneuvers were without effect on the posture of the extremities.

Body Righting Reflexes.—In experiments 4 and 6 a group of postural reactions probably arising in the ligaments and muscles of the spinal column was observed. If the animal was placed on its back, slight rotation of the pelvis about the spinal axis resulted in change of posture of the hindlimbs. Rotation of approximately 15 degrees to the animal's right caused extension of the right hindlimb and flexion of the left; rotation to the left, extension of the left hindlimb and flexion of the right. In the prone position, when the pelvis and lower extremities overhung the edge of a table, abrupt changes in the posture of the forelimbs occurred on rotation of the pelvis. Clockwise rotation of the pelvis with the thighs employed as levers brought about extension of the right forelimb and flexion of the left. In this position the right hindlimb, although its lateral surface was not in contact with the table, occupied the place of the underlying extremity, so that extension of the right forelimb was the response compatible with the postural pattern. If the pelvis was rotated to the left the picture was reversed. These proprioceptive influences are minimal in the lateral position, but are found during the process of righting. Though they do not directly affect the reflex pattern, they create attitudes that conform with it.

Rhythmic Righting Movements.—When a well compensated thalamic animal or a bilateral motor-premotor preparation is turned quickly, even if only a few degrees on its longitudinal axis, the uppermost extremities,

especially the arm, exhibit a series of rapid rhythmic movements. These movements, which undoubtedly arise in part from the labyrinth, may continue for a considerable time after the stimulus, but they cease immediately the hand or foot comes into contact with a graspable object.[2c] When this occurs the limb slowly becomes flexed, and the body in consequence tends to be pulled into the standing position. In experiment 1 these rhythmic righting reactions were present immediately after the final operation; once the horizontal position was achieved, however, the animal was unable to maintain the position and continued to fall back into the thalamic reflex attitude. About two months after the operation the animal was sufficiently well compensated to hold the horizontal position once it had been attained.

These rhythmic righting movements should be carefully distinguished from "groping," a deliberate compulsive movement terminating in prehension, which is cortical in origin and depends on the integrity of the visual system and the pyramidal tracts; it is seen after extensive frontal lesions, usually bilateral, which do not involve the pyramidal system.

THE GRASP REFLEX

The grasp reflex, as observed in the bilateral motor-premotor preparations, is an unvarying reaction so long as the position of the animal remains constant; indeed, it is as definitely predictable as the positive supporting reaction of Rademaker, and, like the positive supporting reaction, it forms a part of a basic postural mechanism. The grasp reflex differs from "forced grasping," as seen in animals (Richter and Hines;[13] Fulton, Jacobsen and Kennard[14]) and in man (Schuster and Casper[15]), in being independent of the pyramidal system and in not being subject to fluctuations from cortical integrations. There can be no doubt, however, that the grasp reflex is the basic subcortical prehension pattern on which the forced grasping phenomenon is built. If this is true, one would expect that forced grasping, like the grasp reflex, would vary in its intensity with the position of the body in space.[16]

13. Richter, C. P., and Hines, Marion: (*a*) The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Research Nerv. & Ment. Dis., Proc. **13**:211-224, 1934; (*b*) Experimental Production of the Grasp Reflex in Adult Monkeys by Lesions of the Frontal Lobes, Am. J. Physiol. **101**:87-88 (June) 1932.

14. Fulton, J. F.; Jacobsen, C. F., and Kennard, Margaret A.: A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys, Brain **55**:524-536 (Dec.) 1932.

15. Schuster, P., and Casper, J.: Zwangsgreifen und Stirnhirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:738-792, 1930.

16. Kennard, Margaret A.; Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity and Vasomotor Disturbance, Brain **57**:69-84 (March) 1934.

In several recently reported cases of premotor lesion in man this has proved strikingly true;[17] i. e., the forced grasping was accentuated by placing the patient in the lateral position with the affected extremity uppermost.

The relation of the grasp reflex to the animal's position in space may be described fully as follows: When the animal is sitting up, and also when in the prone position, the grasp is present in all four extremities. It is absent in all limbs when in the supine posture. With the animal on its right side, the grasp reflex is observed in the left extremities (the uppermost, flexed limbs) and is absent in the right extremities (the underlying, extended limbs). This is illustrated in figure 8. In the left lateral position the picture is reversed. The grasp reflex is present in the right (now the uppermost, flexed) limbs and absent in the left (now the underlying) limbs. Like the thalamic pattern, the grasp can be inhibited in the upperlying extremities by applying pressure to the uppermost body surface, as previously described. Immediately the pressure is relaxed, the grasp reflex reappears. It also appears in the underlying limbs as soon as contact with the table of the dependent body surface is removed. When flexion of one forelimb and extension of the other follow rotation of the pelvis, as already described, the grasp reflex is present in the hand of the flexed forelimb.

A reason for this association between the grasp reflex and the postural reflexes suggests itself when the manner of righting from the lateral position is considered. The first movements in this process are rapid rhythmic movements of the uppermost extremities, which have just been described. Immediately on contact of the palm of the moving hand with any surface suitable for grasping, the rhythmic movements cease, and a firm grasp ensues. By this grasp, together with the contraction of the flexor muscles of the elbow and shoulder, the fore half of the body is brought into the prone position, the hind half rapidly following. The grasp reflex is absent in the underlying limbs, where, because of the dependent position and the associated extension, it would be quite useless for righting. The reflexes arising from torsion of the ligaments and muscles of the spinal column aid in bringing the hind half of the body to the prone posture. From this position standing is facilitated by the various *Stützreaktionen* described by Rademaker.[12]

We infer from these considerations that the grasp reflex at the thalamic level is a part of the righting reflex mechanism, and hence a phase of the righting reflexes peculiar to the primates; at the cortical level the grasp reflex takes on more complex functions, which appear to be integrated primarily by the motor and premotor areas.

17. Wechsler, I. S.; Bieber, I., and Basler, B. H.: Postural Reflexes in Patients with Lesions of the Frontal Lobes, Arch. Neurol. & Psychiat. **35**:1208-1215 (June) 1936.

NECK AND LABYRINTHINE REFLEXES

In one respect the bilateral motor-premotor preparation differs from the thalamic monkey. The body righting reflexes appear to be identical in the two preparations; the neck and labyrinthine reflexes, however, are seldom conspicuous in the bilateral motor-premotor preparation, whereas in the thalamic monkey they are exaggerated. Apparently, therefore, some of the other projection systems from the cortex, probably from the face areas, tend to depress the neck reflexes. No attempt has as yet been made to determine what parts of the cortex are responsible for this difference.

COMMENT

AGE OF ANIMAL AND DURATION OF LESION

No one of the animals that have been described survived complete bilateral ablation of the motor and premotor areas for longer than forty-eight days (experiment 3). In experiment 1 the period of survival was five months, but a small strip of premotor cortex remained intact in one hemisphere, amounting to about one twentieth of the total mass of premotor tissue normally present in the brain. It is undoubtedly significant that this animal continued to improve throughout the five month period and ultimately regained the capacity to stand and to walk (very awkwardly). None of the other animals in the series regained volitional power to this extent; from Kennard's observations [18] on baby monkeys, however, it is obvious that purposeful integrations can occur when the motor and premotor regions are lacking, but it is not yet known whether these integrations are cortical or subcortical in origin. It is probable that if adult animals could be adequately nursed for a sufficiently long period after bilateral motor-premotor ablation they might regain some degree of voluntary power (through the extrapyramidal projections from the frontal, parietal and temporal areas, or from subcortical levels); but it is clear that an adult animal recovers far more slowly than an infant, and it is probable that the ultimate degree of recovery would be far less. It is hoped that some one will succeed in maintaining these interesting preparations alive for a longer period than those just reported.

SPASTICITY AND THALAMIC REFLEX PATTERN

The quality of muscular resistance encountered on attempting passively to manipulate the extremities of an animal exhibiting the thalamic reflex pattern deserves mention. In the lateral position the lowermost extremities are vigorously extended, while the uppermost

18. Kennard, Margaret A.: Age and Other Factors in Motor Recovery from Precentral Lesions in Monkeys, Am. J. Physiol. **115**:138-146 (March) 1936.

extremities exhibit almost equally intense flexor rigidity. We have carefully avoided referring to the flexor or the extensor resistance as "spastic," since the quality of resistance does not conform to that ordinarily associated with the spastic state—i. e., the lengthening and shortening reactions are not readily obtained; the deep (myotatic) reflexes of the digits, though somewhat increased, do not exhibit spreading or the exquisitely sensitive reactions seen after isolated lesions of area 6 or after the strip lesions of the anterior border of area 4 described by Hines.[19] These more restricted cortical lesions appear to release certain discrete elements of the postural mechanism, especially the antigravity muscle of the extremities. It appears that these incomplete lesions are those which give rise specifically to the spastic state.[20] The postural resistance underlying the thalamic reflex pattern represents a far more complete release of subcortical mechanisms; it involves all muscle groups to approximately the same extent, and in these circumstances the excessive exaggeration of myotatic reflexes underlying the spastic state does not occur.

LOCUS OF GRASP REFLEX

Since the grasp reflex forms a part of a fundamental postural reflex pattern, it has become a matter of the greatest possible interest to determine at what level in the primate brain stem this reaction is integrated. Clearly, it is subcortical. The caudate nucleus and globus pallidus appear not to be essential for the reaction, and preliminary studies by Dr. H. G. Widgerson suggest that the reaction is integrated in the brain stem somewhere between the anterior nucleus of the thalamus and the anterior border of the pons.

SUMMARY AND CONCLUSIONS

The neck and labyrinthine reflexes and the righting reflexes of Magnus and de Kleyn are normally suppressed by the cerebral cortex. An attempt has been made in the present study to determine which cytoarchitectural areas of the cortex are responsible for inhibiting these postural reactions in monkeys and baboons. Bilateral ablation of the premotor field (area 6a) fails to release them; primary bilateral ablation of the motor area (area 4) similarly fails, as does removal of both motor areas and one premotor area or vice versa; but when all four

19. Hines, Marion: The Anterior Border of the Monkey's (Macaca Mulatta) Motor Cortex and the Production of Spasticity, Am. J. Physiol. **116**:76 (June) 1936; Motor Cortex, Bull. Johns Hopkins Hosp. **60**:313-336 (May) 1937.

20. Fulton, J. F.: The Interrelation of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions, Medicine **15**: 247-306 (May) 1936; Spasticity and the Frontal Lobes: A Review, New England J. Med. **217**: 1017-1024 (Dec. 23) 1937.

areas, motor and premotor, are removed from both hemispheres of an adult monkey or baboon, the righting reflexes (and occasionally neck and labyrinthine reactions) appear, and the animal exhibits a stereotyped postural pattern identical with that described by Magnus for the thalamic monkey; i. e., when the animal is in the lateral position the undermost extremities are vigorously extended and the uppermost extremities flexed (fig. 8); the uppermost extremities moreover, show a conspicuous grasp reflex. When the animal is turned over, the postural pattern is reversed.

The fact that the grasp reflex forms a part of the thalamic reflex pattern of these bilateral motor-premotor preparations makes it possible to analyze the phenomenon, and the following conclusions concerning its mechanism have been reached.

1. The grasp reflex varies with the position of the body in space, directly with the righting reflexes.

2. The grasp reflex is also to some extent influenced by the neck and labyrinthine reflexes when these are present.

3. The skin receptors are unessential for elicitation of the grasp reflex and evidently play little part in its ordinary production.

4. Stretch of the digital tendons is the most effective stimulus for the grasp; after complete deafferentation of the arm muscles, tension on the shoulder muscles serves to evoke the grasp in an animal exhibiting the thalamic reflex pattern.

5. When the shoulder muscles have, in addition, been deafferented, the grasp can be elicited by moving the animal rapidly through space.

6. Since the grasp varies, as do the other righting reflexes, with the position of the body and since, if the animal succeeds in grasping an object when in the lateral position, the body is drawn automatically into the horizontal posture, it is concluded that the grasp is an integral part of the body righting reflex mechanism.

ADDENDUM.—In a contribution by Walshe and Hunt,[21] which was published after this paper was completed for press, criticism was offered of our conclusion that the grasp reflex is a part of the righting reflex mechanism. Since our evidence had not been published, Dr. Walshe was at a considerable disadvantage, and it is hoped that the present exposition will give him an adequate basis for relevant comment.

Dr. Margaret Kennard assisted in many phases of the work reported on in this paper.

21. Walshe, F. M. R., and Hunt, J. H.: Further Observations upon Grasping Movements and Reflex Tonic Grasping, Brain **59**:315-323 (Oct.) 1936.

EFFECT OF EXPERIMENTAL TEMPORARY VASCULAR OCCLUSION ON THE SPINAL CORD

II. CHANGES IN MINERAL SALT CONTENT OF NERVE CELLS

LOUIS L. TUREEN, M.D.
ST. LOUIS

Previous studies on the nature of cytologic responses in injured nerve cells have demonstrated that functional disturbances precede demonstrable histologic evidences of trauma (Tureen[1]). Normal function, indeed, may be restored before detectable cellular changes appear. Histologic alterations usually persist for a week before the cell resumes its normal appearance.

One phase of the problem under consideration is concerned with chemical changes within the nerve cell during its response to ischemic injury. The method of micro-incineration has been sufficiently standardized to permit its use in comparing mineral salts in experimental and control tissues. In the present state of knowledge one may reasonably be cautious in attempting to identify the residual salts; however, an adequate store of information as to the topographic distribution of salts within tissues and cells can be obtained. This report deals with the study of alterations in the mineral salt content of anterior horn cells of the spinal cord following experimental ischemia. A comparison of such changes with those occurring post mortem in normal anterior horn cells forms the basis of a separate report.[2]

METHOD AND MATERIALS

A method of aortic compression which insures total ischemia of the lower half of the spinal cord has been described in the first of this series of papers.[1] Spinal cords of the same animals (cats) were available for both the histologic

From the Departments of Anatomy and Medicine, Washington University School of Medicine.

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This investigation was aided by grants from the Josiah Macy Jr. Foundation, the C. M. Warren Fund of the National Academy of Arts and Sciences and an appropriation from a grant to Washington University for research in science from the Rockefeller Foundation.

1. Tureen, Louis L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord: I. Correlation Between Structural and Functional Changes, Arch. Neurol. & Psychiat. **35**:789 (April) 1936.

2. Tureen, Louis L.: Postmortem Changes in the Distribution of Mineral Salts in Cells of the Anterior Horn, to be published.

studies, described in the paper already mentioned, and the incineration experiments reported here. Ischemic periods ranged from fifteen to ninety minutes, and the animals were subsequently killed at intervals up to fifty-six days. Sections of the cervical (normal) and lumbar or sacral (ischemic) segments were fixed in absolute alcohol (9 parts) and formaldehyde (1 part), embedded in paraffin, sectioned and incinerated according to the method of Scott.[3] Alternate sections of the series were stained with hematoxylin and eosin as controls. The incinerated tissues were observed with a Zeiss cardioid condenser and a Zeiss homogeneous immersion, 90 numerical aperture, 1.25 mm. achromatic lens fitted with a diaphragm. Illumination was furnished by a Spencer lamp no. 394, fitted with a projection Mazda 500 watt, 115 volt General Electric bulb and without a daylight filter.

OBSERVATIONS AND RESULTS

The material may be considered in two groups: (1) tissue which had been subjected to sublethal periods of ischemia, producing temporary functional and histologic disturbance from which complete recovery eventually resulted, and (2) tissue which had received fatal insult because of prolonged deprivation of blood. It was observed in earlier experiments that irreparable functional and histologic damage followed vascular occlusion of the spinal cord for periods of twenty minutes or more. There was total necrosis of all nerve cells; functional and cytologic recovery, on the other hand, followed vascular occlusion lasting as long as fifteen minutes.

Even under optimum conditions there is considerable variation in the appearance of the incinerated normal anterior horn cells.[4] In general, the ash residue of the well fixed anterior horn cell was seen to be uniformly distributed throughout the cytoplasm as a finely powdered, bluish deposit, usually somewhat less than 1 micron in diameter. It was in the cytoplasmic ash, normally, that the greatest variation occurred. In most cells, for instance, the remains of the Nissl substance were clearly discernible. The color of these deposits was flat white, and careful examination usually revealed a superimposed hue of brownish red. These granules were somewhat larger than those in the cytoplasmic background, and were denser in some cells than in others. Occasional cells did not exhibit clearly defined Nissl deposits. It is yet impossible to assign this variation to a definite physiologic state of the cell. The reason for the normal variations in cytoplasmic ash is obscure, but it is believed that it is not associated with the technical procedure, particularly with fixation. Portions of the spinal cord prepared by the Altmann-Gersh frozen dehydration method (Scott[5]) showed the same general

3. Scott, Gordon H.: The Localization of Mineral Salts in Cells of Some Mammalian Tissues by Micro-Incineration, Am. J. Anat. **53**:243, 1933; A Critical Study and Review of the Method of Microincineration, Protoplasma **20**:133, 1933.

4. Kruszynski, J.: Cytochemische Untersuchungen der veraschten Nervenzell, Bull. internat. Acad. polon. d. sc. et d. lett., s.B, Sc. nat. **3**:105, 1934.

5. Scott, Gordon H., and Williams, P. S.: A Simplified Cryostat for the Dehydration of Frozen Tissues, Anat. Rec. **66**:475, 1936.

characteristics as those fixed with alcohol and formaldehyde. Frequently there was at the periphery of a cell a definite concentration of minerals, which was thought to be due largely to shrinkage of the cell during fixation.

In these, as in most other cells, nuclear minerals were distributed in the same pattern that the chromatin material assumed in the stained sections. On the whole there was relatively little nuclear residue. The nucleolus was represented by a dense mass of flat white deposits, while small scattered masses representative of nuclear chromatin comprised the remainder of the salt.

The axis-cylinder had an ash residue, but the myelin sheath failed to leave any large mineral deposit, since only the neurokeratin network could be discerned. The dendritic processes had the same inorganic constitution as that observed in the cell body, but distinct differences were seen in the axon hillock, which contained little or no mineral salts (figs. 1, *1* and 2, *10*).

Tissues Subjected to Periods of Sublethal Ischemia (Fifteen Minutes).—1. Stage of Progressive Mineralization: Preparations fixed immediately at the end of the ischemic period exhibited slight deviations from the normal. These changes involved only a few cells and consisted principally of diminution in the cytoplasmic mineral deposits, as well as loss of discreteness of the salt residue of the Nissl substance. The salt retained its normal bluish color but in some instances was rearranged within the cell, the perinuclear zone becoming relatively bare and the peripheral zones containing most of the salt. The nuclei appeared to be unchanged. The majority of cells in the field could be considered normal.

At a period seven hours after the restoration of circulation a striking alteration in the picture had occurred. The cells were all shrunken to a pronounced degree and were crowded with large, closely packed, flat white granules of ash residue, which were tinted brownish red. All cytoplasmic detail was abolished; the minerals of the Nissl substance could not be identified. In the majority of cells the nucleus was obscured by the alteration in both the nuclear and the cytoplasmic minerals, which were undifferentiated from each other. In an occasional cell in which the large white mineral deposits were shifted toward the periphery, the central area of the cytoplasm contained a few fine blue granules. In such instances the nucleus became visible by its distinct mineral deposit, which was unusually heavy. Such deposits, though for the most part white, in some cells exhibited a distinctly reddish color (fig. 1, *2*). Normal nuclear formations were not observed before the thirty-six hour stage, and then only rarely. The nucleolus was completely obscured; the deposits filled the greater part of the nuclear space and appeared to spread into cytoplasmic areas (fig. 1, *3* and *4*).

In the twenty-eight and thirty-six hour periods a few necrotic cells were identified by the formless, irregular, heavy ash deposit which they left and which bore only a remote resemblance to the majority of injured cells in the field.

The striking feature at this stage was the appearance, after a preliminary tendency toward loss of minerals, of a heavy and progressive increase in salts which normally do not form the main inorganic constituents of the cell. This anomalous deposition of ash appeared to be at the expense of the usual mineral constituents of the cell, which either had disappeared or were obscured by the massive deposits. By thirty-six hours the excessive mineralization had reached its maximum state.

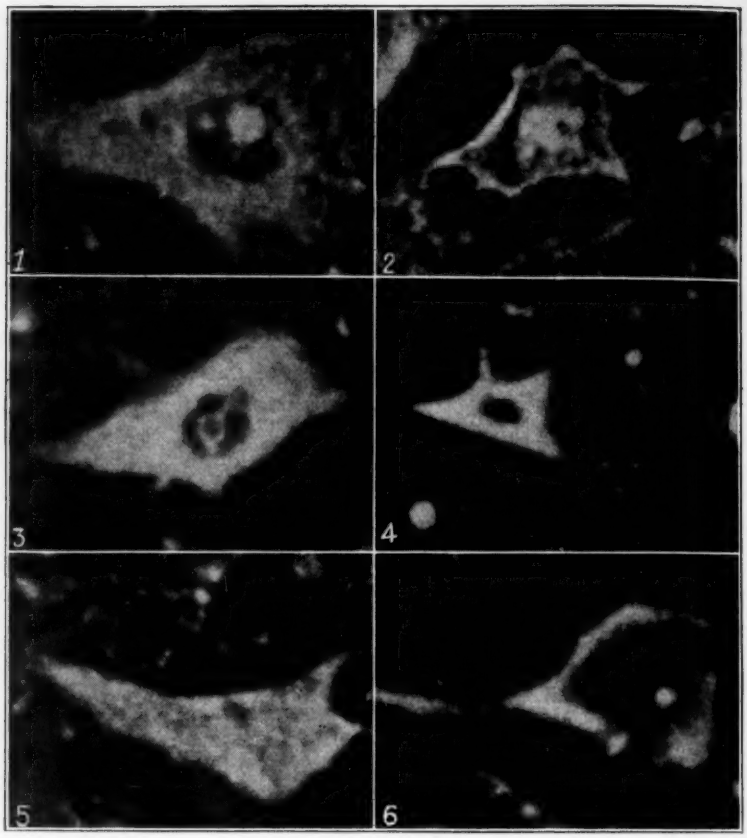

Fig. 1.—Mineral residue in the anterior horn cells of the cat (magnification, 640). In all cells, except that shown in *1*, the vascular occlusion lasted fifteen minutes.

1. Normal configuration of an uninjured cell in the thoracic portion of the cord, demonstrating the flakiness of the Nissl deposits within the cytoplasm, superimposed on a finer granular background. Note the distribution of minerals within the nucleus. The nucleolar deposit is heavy, and smaller masses are scattered in an otherwise bare zone.

2. Cell from the lumbar portion of the cord twenty-eight hours after ischemia. Mineral deposits are distinctly heavier and whiter than normal. In this cell they occupy largely a marginal position. Nuclear minerals are extremely heavy, filling the entire space, obscuring the nucleolus and seemingly spreading into the cytoplasmic zone. These deposits were distinctly brownish. Fine mineral deposits are scattered within the pericellular shrinkage spaces.

3. Cell from the lower part of the thoracic portion of the cord thirty-six hours after ischemia. Cytoplasmic minerals are dense, filling the entire space and obscuring all normal cytoplasmic structures. Nuclear minerals approach the normal in content but continue to occupy a greater portion of the nuclear space than normally.

4. Cell from the lower part of the thoracic portion of the cord forty-eight hours after ischemia. The cell is shrunken and contains a high concentration of cytoplasmic minerals. Note the comparatively large size of the shrinkage space.

5. Cell from the lumbar portion of the cord seventy-two hours after ischemia Cytoplasmic minerals are still heavy. Shrinkage is slight.

6. Cell from the lumbar portion of the cord five days after ischemia. Marked margination of white granules has occurred. Fine blue granules fill the central portion of the cells. The Nissl substance is still absent. Nuclear configuration is approximately that of a normal cell.

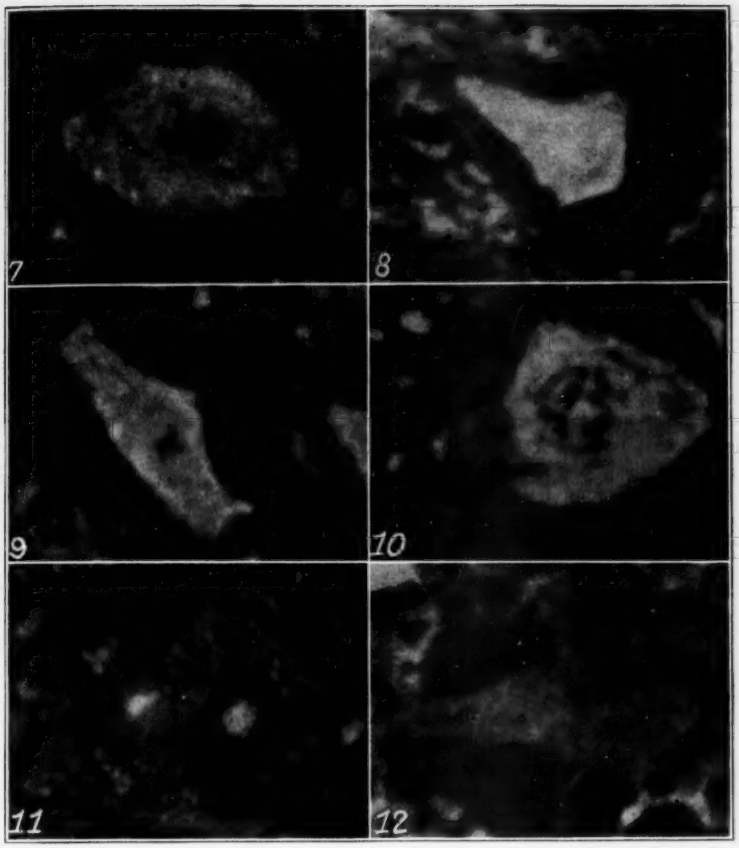

Fig. 2.—Mineral residue in the anterior horn cells of the cat. *7, 8* and *9* show cells from the lumbar portion of the cord subjected to vascular occlusion for fifteen minutes (magnification, 640). *7.* Cell seven days after ischemia. The Nissl substance shows well. The cytoplasmic ash is still brownish white and intermingles with the bluish ash to a large extent. The nucleus is normal.

8. Cell twenty-eight days after ischemia, which is fairly normal except for the heavy mineral deposit.

9. Cell fifty-six days after ischemia. The ash residue is normal in every respect.

10. Normal cell from the cervical portion of the cord (magnification, 640), demonstrating the configuration of minerals within the cytoplasm. Nissl flakes are distinct. Note the mineral deficiency within the axon hillock.

11. Cell from the lumbar portion of the cord thirteen hours after subjection to ischemia for thirty minutes (magnification, 760). There is general demineralization of the cytoplasm, so that it can scarcely be distinguished from the surrounding interstitial spaces. Nucleolar minerals are heavy, and the residue of two neuroglia cells, superimposed on the cytoplasm, is visible.

12. Cell from the lumbar portion of the cord four and one-half hours after subjection to ischemia for sixty minutes (magnification, 640). The profound degree of mineral loss is again demonstrated.

2. Stage of Nuclear Reorganization (from Thirty-Six to Ninety-Six Hours After Ischemia): The nucleus was more easily discernable after the thirty-sixth hour. In a few instances nuclear ash was deposited in normal amounts and formations. In the majority of cells, however, the deposits were heavy and filled much of the nuclear space. Sometimes the tendency for cytoplasmic minerals to marginate made the nuclear deposits visible. More often the decrease in total nuclear salt, leaving clear nuclear spaces, accomplished this. The nucleolus often was completely obscured. The color of the mineral salt tended to be brownish, which indicated the presence of iron. At successive periods the nuclear salt was decreased, until at the fifth day it was generally normal in amount, distribution and color. However, even at later periods an occasional cell showed heavy nuclear mineralization.

The cytoplasmic residue maintained a constantly heavy concentration of the same type of flat white and reddish brown granules (fig. 1, *5*). The tendency toward margination became pronounced at about the fifth day (fig. 1, *6*). When the cell was viewed in cross section, the outer fifth to the tenth portion contained the main mineral deposit, while the perinuclear zone was filled by small blue granules. Cytoplasmic detail was absent, and the Nissl flakes were not represented. The dendritic processes and even the axon hillocks contained the large granular deposits.

A considerable degree of cell shrinkage persisted. The pericellular shrinkage spaces contained a scattering of fine granular deposits.

3. Stage of Restoration of Cytoplasmic Minerals (from Six to Fifty-Six Days After Ischemia): On the sixth day, the first evidence of return of the Nissl substance was the reappearance in some cells of the ash, which became characteristic by the seventh day (fig. 2, 7) and persisted in a relatively normal fashion for the rest of the period of observation. Within the cytoplasmic areas the dominating mineral deposits consisted of large brownish white granules, which were chiefly at the periphery. The marginal zone became narrower as the date of injury became more distant. This condition persisted until the fourteenth day. As the zone of peripheral white ash became smaller, the volume of bluish ash increased, so that eventually this sort of mineral preponderated. At the ninth day a considerable degree of variability was observed in the mineral constitution of individual cells. Some contained greater amounts of one or the other salt; inconstancy in the degree of restoration of Nissl substance and variability in the size of the marginal zone were the rule. In many cells the white granules intermingled freely with the blue. From the fourteenth to the twenty-eighth day the cytoplasmic picture closely approximated that of the normal, although persistence of reddish brown coloration was detected for the first month after injury (fig. 2, *8*). By the fifty-sixth day the majority of cells were normal in the appearance of their mineral constituents (fig. 2, *9*), although an occasional cell exhibited shrinkage and concentration of the ash, in a manner characteristic of degenerative cells.

Interstitial Tissues: These underwent mineral changes only during the period from twenty-eight to ninety-six hours after ischemia. In the earlier stages the capillary endothelial and neuroglia cells showed a normal ash residue. Beginning at twenty-eight hours the deposits became heavier, reaching the greatest degree of concentration between the forty-eighth and the seventy-second hour. Thereafter the mineral concentration decreased, approaching normal at about the fifth day. In this state it continued for the rest of the period of study. It is interesting to note in these experiments that the period of hypermineralization of the inter-

stitial cells was synchronous with the stage of proliferation of the cells.[1] Scott [6] pointed out that rapidly growing cells exhibit a distinct increase in mineral deposits during the period of growth.

The interstitial fluids contained variable amounts of minerals at different stages. No striking alterations were noted in the early stages. The pericellular shrinkage spaces were generally empty. During the second week there was an increasing tendency for brownish white granules to be deposited within these spaces; at the end of the second week the depositions in some spaces were so great that the cell margin was obscured by their proximity. In the second week, also, one found rather large deposits of free iron granules in the interstitial spaces. These appeared to be due to small hemorrhages occurring within the spinal cord.

Tissue Subjected to Periods of Lethal Ischemia (from Twenty to Ninety Minutes).—1. Stage of Hypermineralization: Tissues examined one hour after completion of a thirty minute period of vascular occlusion exhibited, in approximately half the nerve cells of the spinal cord, varying degrees of excessive ash deposits. These consisted of residues of large brownish white granules within the cytoplasm, in which no normal detail remained. The Nissl substance left no recognizable ash. In some cells a deficient quantity of cytoplasmic ash was present, while in others no alterations could be detected. The nucleus was conspicuous in the normal and the mineral-deficient cells but was difficult to identify in cells in which mineral salts were heavily deposited.

A considerable degree of shrinkage of the cells was noted, and the greatest concentration of salt occurred in the most shrunken cells. Ash granules were present in the pericellular shrinkage spaces. The interstitial cells contained slightly increased amounts of mineral salts, while the residue of the interstitial fluids as a whole was diminished.

This stage of hypermineralization was seen only in preparations observed not more than ninety minutes after the beginning of vascular deprivation. All other preparations in this series were observed at later periods and failed to exhibit these changes.

2. Stage of Demineralization: In the tissues subjected to periods of fatal ischemia and fixed at intervals of from one and a half to fifty hours after the beginning of the experiment, a progressive loss of mineral occurred and was terminated only when equilibrium was established between the intracellular and the extracellular salts. The normal cytoplasmic architecture disappeared, leaving only shadowy forms of the cells. At the thirteen hour stage of a specimen subjected to a thirty minute period of ischemia the concentration of cellular salt equaled that of the interstitial fluids, and except for the pericellular shrinkage space the cells were undistinguishable from the background (fig. 2, *11* and *12*). Nuclear deposits were heavier than those in any other part of the cell; they were flat white and moderately massive, while the cytoplasmic and extracellular deposits varied from pale blue to dull brown. Cytoplasmic minerals usually occupied a peripheral position within the cell. At the twenty-eight hour stage free iron granules were scattered abundantly through the tissue spaces, while general dissolution of the tissues had occurred. There was a tendency for the salt to accumulate at the periphery of the tissue block.

Within a small group of cells irregular, dense deposits of minerals occurred in the later stages. No cellular detail could be made out, and the entire mass was

6. Scott, Gordon H.: The Distribution of Inorganic Salts in Adult and Embryonic Cells and Tissues, Cancer Probl., Symposium, 1937, p. 173.

shrunken and the salt concentrated. These deposits resembled closely those seen in tissues at relatively long periods after death.

Altering the duration of the period of total anemia made no material change in the results produced on the mineral content of the nerve cells, provided that the period was twenty minutes or longer. In the early stages after restoration of circulation the cytoplasmic loss of salt was irregular. Portions of the cells might be devoid of mineral while masses of ash were crowded to one side or into the dendritic processes. As the interval after cell death increased the depletion of mineral accelerated. Nuclei appeared conspicuously because of the relative and absolute increase in ash residue. In the last stages of tissue dissolution a few cells tended to exhibit concentration of the minerals in a dense, irregular white mass, characteristic of necrotic cells.

COMMENT

These observations demonstrate that a material difference in the mineral salt content exists between nerve cells which have been subjected to nonfatal injuries and those in which death has been produced by experimental disturbances in circulation. The results suggest that injured cells, after a preliminary and transitory stage of demineralization, become excessively hypermineralized. The normal fine bluish ash deposits are obscured by a heavy layer of large brownish white granules, indicative of the presence of calcium and iron. The normal architectural arrangement of the salt residue is disrupted; the Nissl deposits disappear; the nuclear minerals are masked by heavy depositions within the nucleus and cytoplasm, and the cell becomes shrunken. This state lasts for approximately seven days, when a slow return to the normal mineral structure begins. Some anomalies persist for at least one month after injury, but by the end of the second month neurons show a normal mineral residue.

Fatally injured nerve cells, on the contrary, after a preliminary period of hypermineralization exhibit a progressive loss of minerals, which terminates only when an apparent equilibrium is established between the salts of the cell and those of the tissue fluids.

Associated with both the fatal and the reversible injuries there is an early increase in mineral content of the nerve cells. The difference rests in the rate of dispersion of the excessive salts. Within a few hours after injury the dying cell is significantly demineralized; the recovering cell, on the contrary, continues to accumulate salt and persists in a state of hypermineralization for about two weeks. Observations of early phases of demineralization following ischemic injury show essentially the same stages as those described by Patton [7] in anterior horn cells in association with poliomyelitis: (1) a stage of preliminary decrease, (2) a stage of hypermineralization and (3) a stage of

7. Patton, W. E.: Microincineration of Degenerating Anterior Horn Cells in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **31**:195, 1933.

ultimate demineralization. The first two phases occur after nonlethal injuries; the last two, after lethal injuries, in which case, with more fortuitous timing of observations, it is possible that the first phase might also have been observed. Patton [8] suggested, as he had every reason to do from study of his material, that the state of hypermineralization may be associated with permanent loss of function. This is not supported by the present series of experiments. In the first paper of this series [1] it was shown that a fifteen minute period of ischemia of the lower half of the spinal cord is followed by complete loss of motor and sensory functions of the lower extremities for from one to twenty-four hours. After this period total functional recovery ensues, though slight reflex and tonus changes may persist. At the time that functional recovery is occurring, the anterior horn cells directly concerned with the motor function of the lower extremities are accumulating more mineral salts than were present before injury. This increase in inorganic ash becomes more pronounced during the period that the cell is in a condition of profound cytologic disturbance. Hypermineralization of the nerve cell may be interpreted as evidence of pathologic change in the cell, but at present it cannot be regarded as an index of the functional state.

Decrease in mineral salts, on the other hand, following a brief period during which increase occurs, may be regarded as an almost certain index of cell death. In another paper [9] postmortem disturbances in mineral salts in anterior horn cells were shown to consist of a progressive loss of salts from the cell, which was accelerated by heat and retarded by cold. Although the general behavior of postmortem changes in mineral salts simulated disturbances observed in the fatally injured cells, the time elements were dissimilar. There is a more rapid loss of salt from the cytoplasm in the early stages of ischemic preparations. In the later stages it must be admitted that a similarity exists. It is probable that with the change in permeability of the cell membrane, the salt is diffused into the tissue fluids, where it is carried away by the circulating blood, while in postmortem tissues circulation plays no part.

Changes in injured nerve cells are not demonstrated as readily by ordinary histologic methods as by study of their mineral ash residue. Furthermore, it is not possible by any conventional histologic method to state whether an increase or a decrease in the total minerals has occurred. In the preparations subjected to a fifteen minute period of ischemia, the early stages, characterized histologically as a phase of chromatolysis, represent excessive mineralization, while states described

8. Patton, W. E.: Alterations in Mineral Constituents of Anterior Horn Cells in Experimental Poliomyelitis, Am. J. Path. **10**:615, 1934.

9. Tureen, Louis L.: Post-Mortem Changes in Mineral Salt Distribution in Nerve Cells, Proc. Soc. Exper. Biol. & Med. **35**:293, 1936.

as chromatolysis in tissues undergoing longer periods of ischemia represent demineralization. The Nissl substance could be well followed by the method of incineration, for its disappearance and reappearance coincided accurately in the histologic and in the incinerated preparations. It was observed in the stained tissues that recovered cells colored more intensely with the basic dyes. This coincided reasonably well with the persistence of large white ash deposits in the incinerated material for weeks after recovery.

Little or no correlation between the stages of swelling and demineralization could be established. In the preparations subjected to a thirty minute period of ischemia, both the one hour and the thirteen hour stages are described as exhibiting swelling of the nerve cells; yet the first hour stage showed increase in minerals, while the thirteen hour stage exhibited demineralization.

SUMMARY

The ash residue of anterior horn cells is altered after the spinal cords of cats are subjected to periods of total vascular occlusion. Periods of nonfatal ischemia result in excessive increase in minerals within the nerve cell, which persists in a disorganized manner for about one week. Reorganization of the mineral structure commences in one week and is not complete until after one month. Periods of fatal ischemia result in loss of minerals, which continues until the intracellular and the extracellular salts are equal. Functional activity is regained after sublethal injury at a time when excessive mineralization has begun, and the increase in minerals continues for several days longer. Vascular endothelial and neuroglia cells exhibit hypermineralization at a time when they are most actively proliferating.

Dr. Gordon H. Scott gave assistance in the conducting of these experiments.

DISCUSSION

DR. LEO ALEXANDER, Boston: Dr. Tureen is to be complimented on this thorough study. He has been doing the work in St. Louis, right at the source, where this new method, micro-incineration, found one of its earliest intensive applications. Its completion and perfection were achieved by Dr. G. H. Scott, who also taught my co-workers and me the use of this method, though we were separated from him by a longer distance than was Dr. Tureen. It is gratifying to see that increasing use is made of micro-incineration in histopathologic study. It is an extremely important method, and it does not always simply mirror the information derived from staining. It is a tricky technic, and one must emphasize that it is neither a chemical nor a microchemical method. That some investigators expected too much from it has led to a certain amount of criticism. If it is considered merely a histologic method with a somewhat higher specificity, it is extremely informative. It should be evaluated as are the silver impregnations, for example, which stain specific structures. With incineration specific structures

appear to contain heat-resistant mineral ashes. The minerals which are demonstrated by micro-incineration do not constitute chemical congeries; they are the heat-resistant minerals, as Dr. Scott has already emphasized, while other minerals burn out and disappear. While not constituting a chemical entity, they provide evidence of a histologic entity.

Dr. Tureen has shown, and I think it is extremely important, that the cells appear hypermineralized while they are recovering and become demineralized at their death. We can confirm this from our own studies; in general, one may say that the presence of this ash is correlated with metabolic activity.

In the ganglion cell disease tuberous sclerosis, which is a blastomatous disease with active, tumor-like growth of the affected cells, the cell bodies are rich in heat-resistant mineral ashes. In contrast to this, in the ganglion cell disease amaurotic idiocy, which is a regressive cell disease with lipoid degeneration leading to metabolic inactivity and death of the affected cells, the cell bodies are depleted, most of them being completely deprived of heat-resistant mineral ashes.

Dr. Tracy Putnam, Boston: I should like to ask Dr. Tureen if he can compare the changes observed by this method with the evidences of any pathologic states. How does it compare, for example, with the changes in the cells of the cortex in dementia paralytica or the ventral horn cells in the muscular atrophies?

Dr. Wilder Penfield, Montreal, Canada: I wish to ask Dr. Tureen if he can tell how long the spinal cord will withstand ischemia. Will the tissue of the cord withstand ischemia better than the cerebral tissue?

Dr. Emanuel Friedman, New York: I should like to ask Dr. Tureen whether he finds any varying vulnerability at different levels of the cord.

Dr. Hugh Mella, St. Cloud, Minn.: Dr. Friedman asked about any variability at different levels of the cord; I should like to ask if any notation was made as to the vulnerability of the sympathetic cells in the lateral horn as compared with that of the ventral horn cells.

Dr. Louis L. Tureen: I wish to state that this method, as Dr. Alexander has pointed out, is tricky and one must exercise extreme care in interpreting the results. For example, in another study I found that mineral loss occurs post mortem and that the tissue must be fixed immediately after the death of the animal in order to eliminate artificial results.

The changes which I observed and have reported here were compared with the histologic preparations which formed the basis of a previous paper; the materials were taken from the same cats at the same time that the first preparations were made. I found that the method of micro-incineration is somewhat more delicate in demonstrating cell changes than the orthodox histologic methods. For example, although the histologic preparations showed what in general I called chromatolysis, at stages in which cells were dead or just sublethally injured, the method of micro-incineration revealed in each instance a rather different mineral ash picture; that is, in the dead cell, even though a state of chromatolysis was recognizable histologically, minerals were lost, whereas in the living but injured cell, the minerals were increased, though chromatolysis was also observed.

My co-workers and I observed that with periods of ischemia five minutes longer than the fifteen minute periods which we used there was irrecoverable injury so far as the functional and histologic state of the spinal cord was concerned. On the other hand, a fifteen minute period of ischemia was invariably followed by motor and sensory recovery of the hindlimbs of the cats, and the histologic demonstration was in line with that; longer periods were fatal.

As to the question of the changes at various levels of the spinal cord: In preliminary experiments we demonstrated by the injection of neutral red a definite level of ischemia occurring in a midthoracic region; that is, injection of neutral red showed the level to which the blood would return after the circulation was halted. I did not have an opportunity to compare the lumbar and the thoracic region for the degree of injury, but it is my general impression that there was little difference, provided the circulation was completely cut off. As I say, we proved the ischemic zone by determining the level below which the neutral red was not carried.

It is my impression, although we have not made a special study, that the ventral horn cells are the most vulnerable of the spinal cord. I was impressed by the fact that the lateral horn cells seemed to be more resistant to the ischemia. I cannot say anything about the sympathetic cells. I did not pay particular attention to their condition.

HISTOPATHOLOGIC CHANGES IN THE BRAIN IN EXPERIMENTAL HYPERINSULINISM

ARTHUR WEIL, M.D.

ERICH LIEBERT, M.D.
AND
GERT HEILBRUNN, M.D.
CHICAGO

The application of the insulin shock therapy in the treatment of dementia praecox by Sakel [1] has brought forward anew the problem of the toxic effect of insulin on the central nervous system. The same problem before had interested the clinician and the pathologist when insulin was introduced for the treatment of diabetes mellitus. Over fifteen years of experience has shown that the average doses which are used to reduce the glycosuria seemingly do not produce marked deleterious effects on the central nervous system. However, there is a great difference between the treatment for diabetes mellitus and that for dementia praecox. In the latter case large, toxic doses, which produce convulsive states, are administered daily for as long as from two to three months.

Cases have rarely been reported in which the patient died in hypoglycemic shock after the treatment for diabetes mellitus. Sigwald [2] had collected twenty-six cases up to 1932. Neuropathologic investigation in such cases had not been intensive, except for autopsies in Wohlwill's two cases.[3] In his first case, a woman aged 62, with diabetes of two years' duration, had received 110 units each day for three days and died in deep coma. The brain was dry and brittle; there were generalized severe disease of the ganglion cells (liquefaction), ameboid changes in the astrocytes and swelling of the axis-cylinders. Similar generalized disease of the neurons and astrocytes was observed in the second case. Wohlwill did not see any vascular lesions, in contrast to the observa-

From the Institute of Neurology, Northwestern University Medical School, and the Elgin State Hospital.

1. Sakel, M.: Neue Behandlungsmethode der Schizophrenie, Vienna, Verlag M. Perles, 1935.

2. Sigwald, J.: L'hypoglycémie, Paris, Gaston Doin & Cie, 1932.

3. Wohlwill, F.: Ueber Hirnbefunde bei Insulin Ueberdosierung, Klin. Wchnschr. **7**:344, 1928.

tions of Ehrmann and Jacoby,[4] who described subarachnoid and small cerebral hemorrhages in nine of twelve cases in which the patient died in hypoglycemic shock. Such changes, however, cannot be attributed to the effect of insulin alone, which acted on an already diseased brain. Besides, in all twelve cases "parenchymatous nephritis" was reported at autopsy. It is known, furthermore, from the reports of Fernbach [5] and Elias and Goldstein [6] that patients suffering from organic cerebral disease are much more sensitive to the effect of insulin than the average patient. Bodechtel [7] saw edema of the brain in a diabetic patient aged 41 who had received from 20 to 30 units of insulin three times daily. Microscopically, he observed severe changes in the entire cortex and the striatum, with diminution in the number of cortical neurons, shrinkage of cells and homogenization.

Cases in which nondiabetic patients died after hyperinsulinsim are of greater value for our investigation. Teerbruegge [8] reported such a result in a case of multiple adenomas of the pancreas. He described diffuse acute disease of the ganglion cells, without glial proliferation, and mild, perivascular hemorrhages. De Morsier and Mozer [9] reported the autopsy observations in the case of a morphine addict, aged 41, who had given himself daily injections of as much as 100 units of insulin. After one of these massive injections he was found in a comatose condition. Despite large doses of dextrose, he could not be aroused, and died on the third day. Microscopically, small subarachnoid hemorrhages were seen. The cortical neurons were shrunken; their cytoplasm was pale and reduced in volume; the nuclear outlines were hazy, and the nucleoli had disappeared. There was marked glial proliferation, which was most pronounced around blood vessels, the perivascular spaces of which were widened.

The problem of the toxic effect of insulin on the central nervous system has been approached experimentally in various publications.

4. Ehrmann, R., and Jacoby, A.: Ueber Blutungen bei mit Insulin behandelten Komafällen, Deutsche med. Wchnschr. **50**:138, 1924; Klin. Wchnschr. **4**:2151, 1925.

5. Fernbach, J.: Die Insulinempfindlichkeit bei Hirnerkrankungen, Ztschr. f. klin. Med. **122**:595, 1932.

6. Elias, H., and Goldstein, J.: Insulinschock und Zentralnervensystem, Med. Klin. **28**:542, 1932.

7. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, Deutsches Arch. f. klin. Med. **175**:188, 1933.

8. Teerbruegge, A.: Anatomischer Befund bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome, Beitr. z. path. Anat. u. z. allg. Path. **88**:37, 1932.

9. de Morsier, G., and Mozer, J. J.: Lésions cérébrales mortelles par hypoglycémie, Ann. de méd. **59**:474, 1936.

Stief and Tokay [10] injected daily increasing amounts of insulin into four rabbits and four dogs for from eight to eleven weeks. They observed diffuse severe disease of the ganglion cells with paling of the neurons, liquefaction and vacuolation of the cytoplasm and shrinkage. In some areas of the cerebral cortex large fields were deprived of neurons; occasionally, softening and reactive mesenchymal proliferation were noticed. There was regularly marked widening of the meningeal and cerebral vessels, with occasional subarachnoid hemorrhages. In more acute experiments Schereschewsky and his co-workers [11] injected up to 500 units into dogs. They observed pericapillary hemorrhages, vacuolation and shadow formation of neurons in limited areas. Gozzano [12] claimed that 3 units of insulin per kilogram of weight is sufficient to kill a rabbit within twenty-four hours. He described after such short periods severe disease of the ganglion cells throughout the central nervous system. Duenner, Ostertag and Thannhauser [13] briefly reported on insulin intoxication in dogs. The most pronounced changes within the brain were "tremendous" proliferation of the vascular endothelium and new formation of capillaries. Occasionally, hemorrhages and softening of the brain were observed. Tani [14] produced acute and chronic insulin intoxication in rabbits and observed diffuse, degenerative changes in the ganglion cells, with glial proliferation, sclerosis of the cornu ammonis and softening in the substantia nigra. The more recent experiments of Schmid [15] with rabbits were stimulated by the insulin shock treatment. Like Tani, he interrupted the shock by injection of solutions of dextrose. In contrast to the result obtained by the authors previously cited, he observed mild histopathologic changes only, in the form of mild swelling of the neurons and staining of their dendrites, with mild gliosis. He expressed the belief that the insulin shock treatment for dementia praecox does not produce any irreversible changes in the central nervous system.

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10. Stief, A., and Tokay, L.: Beiträge zur Histopathologie und Pathogenese der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**: 434, 1932; **153**:561, 1935.

11. Schereschewsky, N. A.; Mogilnitzky, N., and Gorjaewa, A. W.: Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, Endokrinologie **5**:204, 1929.

12. Gozzano, M.: Alterazioni istologiche del sistema nervosa nell'intossicazione da insulina, Boll. d. Soc. ital. di biol. sper. **4**:73, 1929.

13. Duenner, L.; Ostertag, B., and Thannhauser, S.: Klinik und pathologische Anatomie der Insulinvergiftung an Tieren, Klin. Wchnschr. **12**:1054, 1933.

14. Tani, N.: Experimentelle Beiträge zum Insulinkrampf, Psychiat. et neurol. jap. **39**:5, 1935; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **80**:30, 1936.

15. Schmid, M. H.: L'histopathologie du choc insulinique, Ann. méd.-psychol. (pt. 2) **94**:658, 1936.

In view of these conflicting statements, we decided to study the effect of hyperinsulinism experimentally, in close imitation of the clinical procedure in the treatment for dementia praecox.

MATERIAL AND METHODS

Altogether, twenty-five rabbits were used in the experiments. The brains of fifteen rabbits were studied histologically and compared with those of seven animals used as controls. Of the latter, three were normal rabbits; one had been given injections of bromide solutions, and three had been used in experimental production of syphilis. Two of the brains had to be discarded on account of post-

TABLE 1.—*Duration of Experiments, Units of Insulin Given and Number of Seizures* *

Rabbit No.	Weight, Gm.	Duration of Experiment, Days	Total Units of Insulin	Units of Insulin Producing Seizures			Number of Seizures	Survival#
				Maximum	Minimum	Mean‡		
1	2,700	24	92	12	10	4.1	3	D
2	3,350	22	76	10	4	2.1	15	D
3	3,375	46	216	12	5	2.4	36	D
4	3,020	45	394	15	8	3.5	30	D
5	4,300	57	348	16	6	2.0	40	D
6	3,775	67	402	12	6	2.1	46	80 K
7	2,700	23	157	12	8	3.7	19	D
8	2,100	65	59	3	0.5	0.9	45	11 K
10†	2,000	30	63	4	4	2.0	1	D′
12	2,575	48	207	12	8	3.5	19	68 K
16	2,600	14	13	4	3	1.4	5	5 D′
17	2,565	21	28	10	6	2.9	4	D
21†	2,600	1	55	..	..	7.7	1	K
24	2,960	14	73	6	5	1.8	20	8 K
25	2,925	8	46	6	5	2.0	8	8 K

* In this table only rabbits are included the brains of which were investigated histologically.
† To rabbit 10 sodium bromide was given together with insulin; the duration of the experiment with rabbit 21 was one day, and blood was taken every hour for determination of the blood sugar.
‡ The mean is expressed in units per kilogram of body weight.
# D indicates that the rabbit died during a seizure; D′, that the animal was found dead in the cage, and K, that it was decapitated.

mortem changes; the animals (rabbits 10 and 16) had been found dead the morning after an injection of insulin.

During phase 1 gradually increasing doses of insulin were injected intramuscularly until a dose had been found which would produce a convulsive seizure. As soon as the convulsion occurred, 50 cc. of a 25 per cent solution of dextrose was given by stomach tube, or from 4 to 10 cc. of a 50 per cent solution was injected intravenously. In phase 2 this convulsion-producing dose was given daily, except on Sundays during periods which varied for different animals (table 1). The number of units which was required to produce a seizure varied from a maximum of 3.1 per kilogram of body weight to a minimum of 1.8, with a mean of 2.5. In an exceptional case (rabbit 8) as few as 0.25 units per kilogram was sufficient to start a seizure. As a rule, the rabbits soon became sensitized to the effect of insulin, and after a week of seizures the number of units could usually be reduced to one half or two thirds of the original dose. However, after two

or three weeks of seizures resistance seemed to appear, and the units had to be increased to the original number. The convulsions were noticed usually toward the end of the second hour and were preceded by a mild comatose state. During the seizure the pupils were maximally dilated; there was hypersalivation; no reaction to painful stimuli occurred, and the *Stützreflex* was absent. Frequently, two or more seizures were noticed during the short interval between the first attack and the stomach feeding or the injection of the sugar solution. Six rabbits (1, 2, 3, 5, 7 and 17) died suddenly during a seizure—four after from twenty-one to twenty-four days of treatment and the other two after forty-six and fifty-seven days, respectively. One (rabbit 4) died five hours after a seizure.

The brains were fixed in a solution of formaldehyde immediately after death following a seizure or after the rabbit had been killed by decapitation. Both pyroxylin and paraffin sections were prepared and stained with cresyl violet, Van Gieson's method, Davenport's method for axis-cylinders and Weil's method for myelin sheaths. Frozen sections were stained for fat, microglia (Kanzler) and astrocytes (Cajal). In order to facilitate a comparative study, the nomenclatures of Winkler and Potter [16] and Rose [17] were used. As in the human brain, the cornu ammonis seemed to be a sensitive indicator of the influence of insulin on the cerebral neurons. Of course, comparisons with pathologic changes in the human brain can be made only in a superficial way. While in the rabbit h_5, h_4 and, to a lesser degree, h_3 are most affected in hyperinsulism, in man Sommer's sector is most involved in various pathologic conditions, i. e., the lateral arch of the curvature of the cornu ammonis, which includes h_1 and h_2 (Bratz [18] and Bodechtel [19]). For comparative studies of the cerebral cortex the precentral and postcentral areas were selected (areas 1 + 3 and 4). Here, the changes were most pronounced in laminae V and VI, though the other laminae, too, were involved. In addition, the striatum, thalamus and cerebellum were studied in detail. The pathologic rating in table 2 is a mean obtained from the study of these six structures.

HISTOLOGIC REPORT

A short abstract of the microscopic reports follows.

RABBIT 1.—The microscopic changes were mild. There was some pale staining of the cytoplasm of the neurons in the lower lamina of the cerebral cortex, with folding of the nuclear membrane. A similar picture was seen in the striatum and thalamus and in h_5 of the cornu ammonis. The Purkinje cells of the cerebellum showed a mild degree of homogenization.

RABBIT 2.—There were no pathologic changes of any significance in the cortical neurons, the striatum or the thalamus. Layer h_5 of the cornu ammonis contained

16. Winkler, C., and Potter, A.: An Anatomical Guide to Experimental Researches on the Rabbit's Brain, Amsterdam, W. Versluys, 1911.

17. Rose, M.: Cytoarchitektonik und Myeloarchitektonik der Grosshirnrinde, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 1, p. 635; Cytoarchitektonischer Atlas der Grosshirnrinde der Kaninchens, J. f. Psychol. u. Neurol. **43**:352, 1931.

18. Bratz, E.: Das Ammonshorn bei Epileptikern und anderen Hirnkranken, Monatschr. f. Psychiat. u. Neurol. **47**:56, 1920.

19. Bodechtel, G.: Die Topik der Ammonshornschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:485, 1930.

a larger number of shrunken cells. Many Purkinje cells with homogenization were observed in the cerebellum.

RABBIT 3.—There was vacuolation of the cytoplasm of the neurons of lamina V and VI of the cerebral cortex, with occasional formation of shadow cells, pyknosis of the nuclei and mild glial proliferation. In the striatum and thalamus there was mild shrinkage of the cytoplasm of the different cell types, with occasional neuronophagia. In the cornu ammonis h_4 and h_5 showed marked shrinkage and fragmentation of the neurons, with mild tissue necrosis in some areas and a mild degree of gliosis. The outer branch of the fascia dentata was atrophic and contained small and shrunken cells. There was mild hyperchromatic staining of the Purkinje cells of the cerebellum.

RABBIT 4.—There was severe disease of the ganglion cells throughout the cerebral cortex, most marked in laminae V and VI, with diminution in the number of cells, vacuolation, ischemic disease of the ganglion cells and shrinkage of the remaining neurons. The nuclei were mostly shrunken and stained intensely; the outlines of the nucleoli were irregular. There was no marked gliosis. Similar pictures were seen in the striatum, the thalamus, h_5, h_4 and h_3 of the cornu ammonis and the subiculum, with partial necrosis of tissue but no glial proliferation. There was some homogenization of the Purkinje cells in the cerebellum.

RABBIT 5.—The neurons of the cerebral cortex showed changes similar to those seen in rabbit 4, but to a more marked degree. The diminution in the number of cells was more pronounced and the number of shadow cells larger (fig. 1). In the striatum and thalamus marked shrinkage of the neurons and vacuolation of the cytoplasm were present, without glial proliferation or neuronophagia. In the cornu ammonis the cerebellar changes were similar to those seen in rabbit 4.

RABBIT 6.—There was diminution in the number of neurons throughout the cerebral cortex, with marked shrinkage of both the cytoplasm and the nuclei and mild gliosis (fig. 2 *B*). In preparations stained with Cajal's gold-sublimate method the processes of the astrocytes showed incrustation with numerous fine, dark-staining granules. Both the large and the small ganglion cells of the striatum were markedly shrunken and contained dark-staining cytoplasm. Their nuclei stained pale; the outlines of the nucleoli were indistinct, and their chromatin showed fragmentation (fig. 3 *B*). The cornu ammonis was severely diseased; h_4 and h_3 were atrophic, and the remaining cells were shrunken and darkly stained, containing shrunken nuclei with folded membranes (fig. 4 *C*). There were severe pathologic changes in the subiculum, with neuronophagia of many diseased neurons. The Purkinje cells of the cerebellum and the neurons of the cerebellar nuclei showed marked shrinkage.

RABBIT 7.—In the cerebral cortex there were a number of shadow cells and widespread shrinkage of the cytoplasm and nuclei of the neurons of laminae V and VI. The neurons of lamina III showed marked shrinkage and hyperchromatic staining of both the cytoplasm and the nuclei. In the striatum and thalamus there were mild pyknosis and isolated vacuolation of neurons. In the cornu ammonis, h_5 was mostly involved, and the outer part of the fascia dentata showed marked shrinkage of the ganglion cells and mild gliosis. In the subiculum one saw homogeneous staining of the cytoplasm of its neurons, with mild pyknosis.

RABBIT 12.—There was marked shrinkage of the neurons throughout the cerebral cortex, especially in laminae II, III and IV, which already normally contained

many dark-staining ganglion cells. In laminae V and VI there were shadow cells, besides shrunken neurons. There was mild increase in glia nuclei, with incrustation of the processes of the astrocytes. The changes in the striatum and thalamus were relatively less severe than those in the cerebral cortex, with a mild degree of

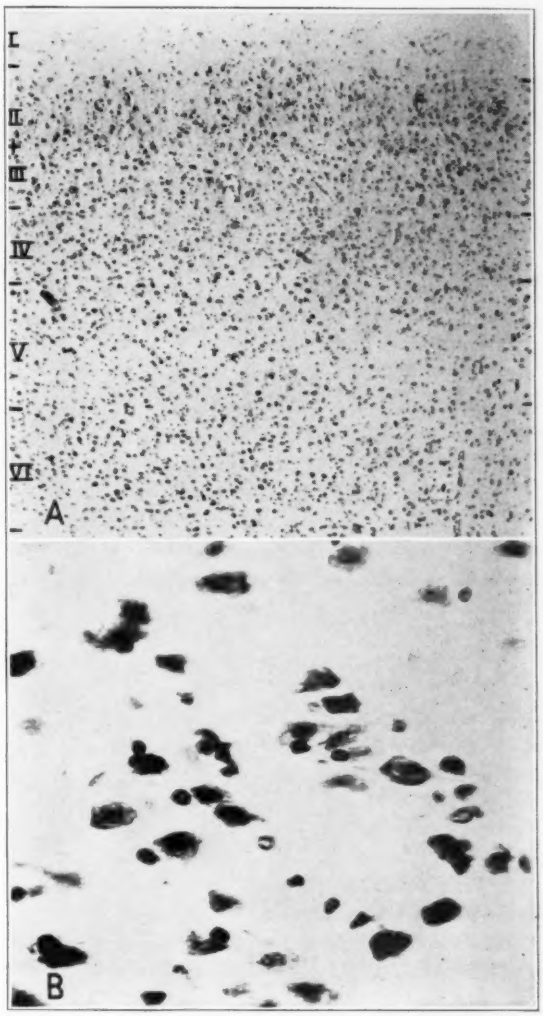

Fig. 1.—Area parietalis (5 and 7) of rabbit 5 which received 348 units by injection during fifty-seven days and died during a convulsive seizure. In *A* there is marked diminution in the number of neurons, most pronounced in laminae V and VI (original magnification, 60). *B* demonstrates severe disease of the neurons of lamina VI (original magnification, 650), with ischemic disease of the ganglion cells, liquefaction, shrinkage and formation of shadow cells.

pyknosis. In the cornus ammonis h_5, h_4 and h_3 showed marked shrinkage of their neurons with some diminution in number, shadow cells and granulation of the nuclei in h_3. The lateral arch of the fascia dentata was atrophic (figs. 4 *B* and 5 *B*). There were some shrinkage and neuronophagia of the neurons of the subiculum. Many shrunken and dark-staining Purkinje cells were seen in the cerebellum.

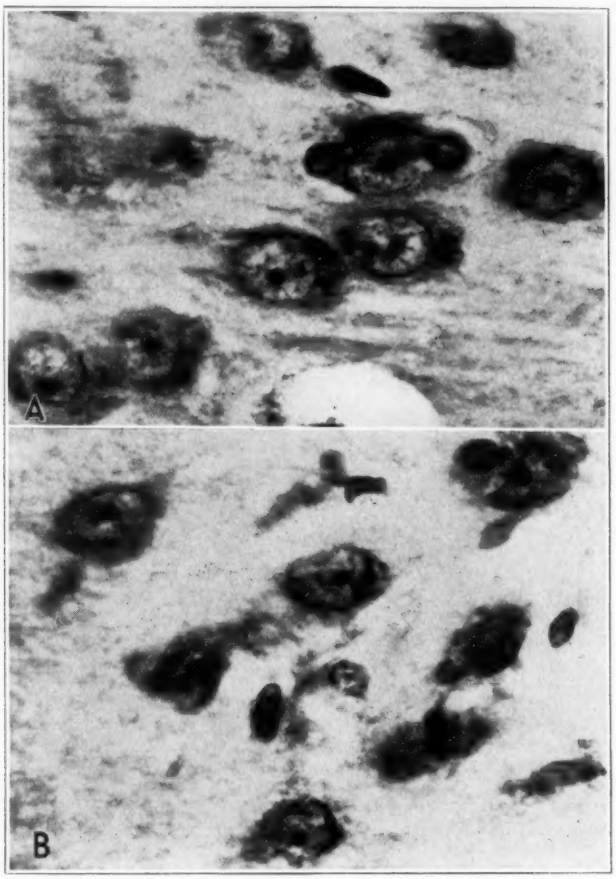

Fig. 2.—Sections through lamina IV of the precentral gyrus, showing a severe degree of shrinkage of the cytoplasm and nuclei (cresyl violet stain; original magnification, 1,300). *A* is from a normal rabbit, and *B*, from rabbit 6 (see text; fig. 4).

Rabbit 24.—There were paling of the cytoplasm and vacuolation of the neurons of laminae V and VI of the cerebral cortex, together with mild gliosis. A similar picture, with homogenization and shrinkage of the nuclei, was seen in the striatum and thalamus. In the cornu ammonis most of the changes, namely, shadow cells,

shrinkage and fragmentation, were observed in h_3. A similar but somewhat less severe picture was present in h_5. The fascia dentata was atrophic in its ventral part. In the cerebellum most of the Purkinje cells were shrunken and stained intensely.

Comment.—Frozen sections from the various brains stained with sudan III did not show fatty degeneration of the diseased neurons. The histologic pictures indicated rather atrophy of the cells without the formation of lipoid abbau products.

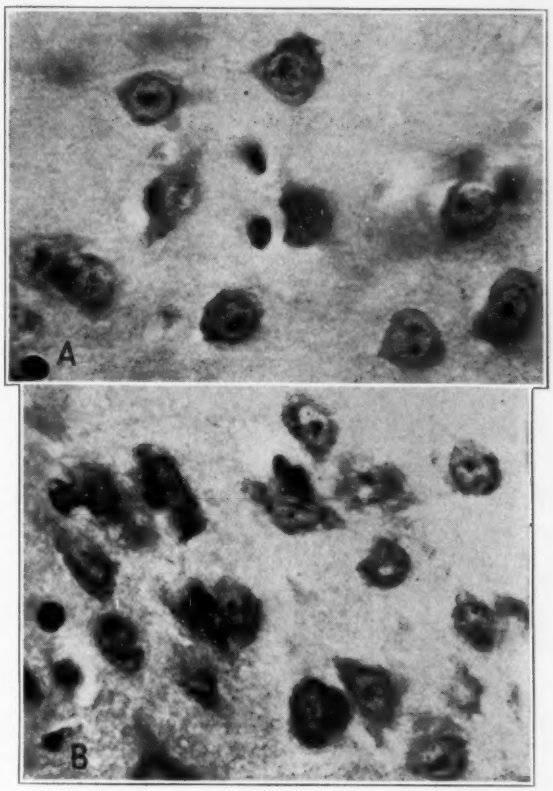

Fig. 3.—Sections of the striatum, showing a marked degree of shrinkage of the cytoplasm, pale staining of the nuclei and fragmentation of nucleoli (cresyl violet stain; original magnification, 1,150). *A* is from a normal rabbit, and *B*, from rabbit 6 (see text; fig. 4).

It is interesting to note that in the brain of rabbit 8, which did not show disease of the cerebral neurons, there was marked proliferation of astrocytes, with the formation of large, intensely staining processes (fig. 5 *C*). This animal had been under treatment for sixty-five days, nearly as long as rabbit 6, the brain of which showed marked histopathologic changes. In rabbit 8, however, as few as 0.25 units per kilogram had been sufficient to produce a convulsive seizure, and the total

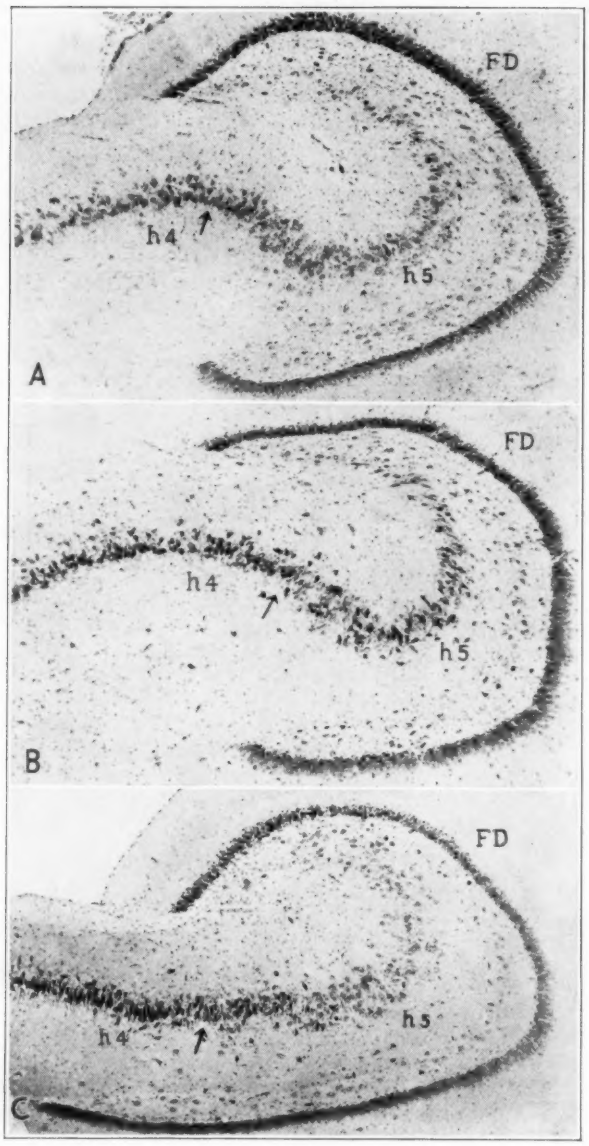

Fig. 4.—Sections through the cornu ammonis with the fascia dentata (cresyl violet stain; original magnification, 100). *A* was taken from a normal rabbit, and *B*, from rabbit 12, in which 207 units was injected during forty-eight days, the period of survival being sixty-eight days. Severe pathologic changes are shown in the lower arch of the fascia dentata (*FD*), in h_5, h_4, h_3 and the subiculum (see text). *C* was taken from rabbit 6, in which 402 units was injected during sixty-seven days, with a survival period of eighty days. There were severe disease of the ganglion cells and atrophy of h_3, h_4, the fascia dentata (*FD*) and, to a lesser degree, h_5 (see text). The arrow indicates the transition between h_4 and h_5.

amount of insulin injected during two months had been 59 units, as compared with a minimum seizure dose for rabbit 6 of 1.6 units per kilogram and a total of 402 units.

Vascular changes were mild, even in the cases in which the duration of the experiment was longest. In rabbits 4, 5, 6 and 12 there was some swelling of

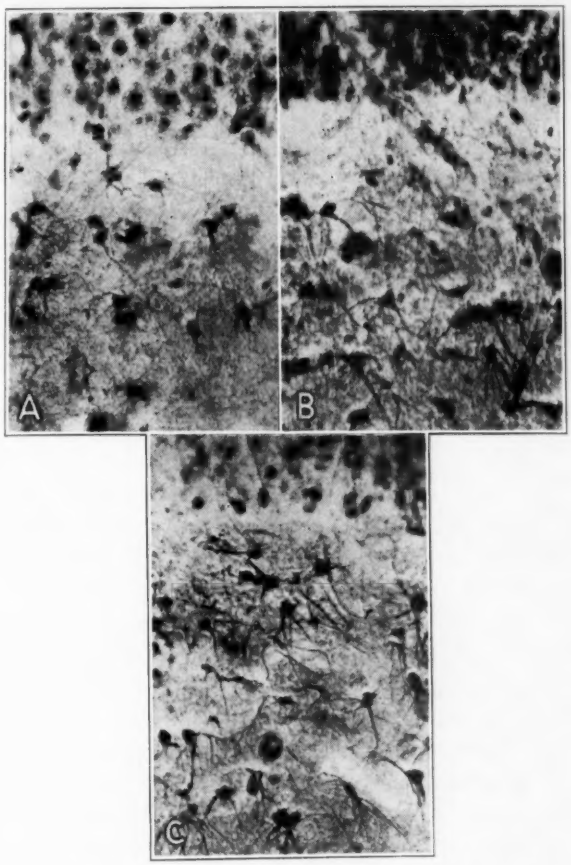

Fig. 5.—Area of the cornu ammonis between the fascia dentata and h_3 (Cajal gold-sublimate preparations; original magnification, 360). *A* is from rabbit 1, in which 92 units was injected within twenty-four days; *B*, from rabbit 12, in which 207 units was injected within forty-eight days, and *C*, from rabbit 8, in which 59 units was injected within sixty-five days. With longer duration of the experiments there is more marked proliferation of macroglia cells, with formation of large, darkly stained processes.

the endothelium, with mild increase of fibroblasts and occasionally hyalinization of the walls of the smaller arteries. In none of the animals, however, was there observed proliferation of capillaries or damage of the walls of the vessels leading

to perivascular hemorrhages. In rabbit 16 alone were there widely spread subarachnoid and scattered cerebral hemorrhages. However, this rabbit had died overnight, five days after the last injection of 4 units of insulin.

In three cases (rabbits 4, 17 and 24) a more advanced stage of encephalitozoötic encephalitis was observed. This chronic form of encephalitis produces pathologic changes usually in the direct environment of the granulomas only. It could not be responsible for the widespread disease of the neurons already described, for in two rabbits with marked encephalitis used as controls none of these changes was noticed (figs. 2 *A*, 3 *A* and 4 *A*).

In none of the experiments was demyelination observed. There were swelling and beginning fragmentation of myelin sheaths in the areas of severe disease of the ganglion cells, together with swelling of the axis-cylinders. Inflammatory reactions were not seen, except in the cases of chronic encephalitozoötic encephalitis, and there was no proliferation of mesenchymal tissue.

The histopathologic changes in these rabbits are summarized and evaluated in table 2.

TABLE 2.—*Summary of Experimental Data and Pathologic Changes in Rabbits Subjected to Insulin Shock*

Rabbit	17	25	21	8	24	2	1	7	12	3	5	4	6
Total number of units	28	46	55	59	73	76	92	157	207	216	348	394	402
Mean number of units	2.9	2.0	7.7	0.9	1.8	2.1	4.1	3.7	3.5	2.4	2.0	3.5	2.1
Number of seizures	4	8	1	45	20	15	3	19	19	36	40	30	46
Pathologic rating*	—	—	—	—	+	(+)	(+)	+	++	+	++	++	++

* In the table — indicates absence of pathologic changes; (+), mild changes (mild ischemic disease of the ganglion cells and homogenization); +, more marked changes (shadow cells, vacuolation, pyknosis and shrinkage), and ++, very marked changes (diminution in number, necrosis of tissue, marked shrinkage and neuronophagia).

COMMENT

In table 2 the cases have been arranged according to the total number of units of insulin which were injected. It is evident that in the rabbits which received the largest number of units there were the most marked histopathologic changes. With doses up to approximately 60 units, even if injected during one day, visible disease of the neurons was not produced, though one might point out that rabbit 21 was killed immediately. After injections of from 70 to 150 units somewhat more marked changes were seen, and if from 200 to 400 units was injected, severe damage was produced in the rabbit's brain.

The instance of rabbit 8, with forty-five seizures and a total of 59 units, as compared with rabbit 12, with nineteen seizures and a total of 207 units, proves that the number of seizures alone is without significance as an indicator of the histopathologic changes. What counts is the cumulative effect of repeated injections of large single doses of insulin.

It would be of interest to apply this observation to the insulin treatment for dementia praecox. If, as many observers have claimed, it is essential for a good therapeutic effect to produce frequent deep coma with seizures, one should avoid the dangerous result of the cumulative

effect of large doses of insulin by using smaller doses and activating them by simultaneous injection of saline solutions or serum or by other means.

One might point out, of course, that it is not permissible to apply observations made on rabbits to the human brain. Rabbits are usually more sensitive to the toxic effect of drugs. On the other hand, the histopathologic observations in cases in which the patient died in hypoglycemic shock, either during insulin treatment for diabetes mellitus or other forms of hyperinsulinism, have been much like those observed in our own experiments. Widespread disease of the cerebral neurons was the rule in such cases, with severe disease of the ganglion cells in the form of liquefaction, vacuolation and homogenization. Our results also resemble closely those obtained by Stief and Tokay [10] in rabbits and dogs. We did not observe the severe subarachnoid and cerebral hemorrhages which have been reported in diabetic patients and which occur in acute experiments on animals when massive doses of insulin are injected.

There is a definite difference between the histopathologic picture of the brain of animals (rabbits 3, 4 and 5) which died during a convulsive seizure after a long period of injections and that of animals (rabbits 6 and 12) which survived for as long as eighty days. While in the first group ischemic disease of the ganglion cells, vacuolation and homogenization were predominant (fig. 1 *A* and *B*), shrinkage of the cytoplasm and nuclei were the outstanding features in the second group. Rabbit 24, which lived for eight days after two weeks of treatment, may be considered as representing a transitory stage between the two groups.

A peculiar staining reaction was observed in sections stained for myelin sheaths (Weil method). The neurons of the parts of the cornu ammonis which were most severely affected stained deep black, together with the diseased sector of the fascia dentata. Both are the structures of the rabbit's hippocampal formation which are closest to the outer surface of the gyrus, next the subarachnoid spaces, from which they are separated by loose tissue structures only, and not by dense layers of myelinated fibers, as is the rest of the cornu ammonis. The problem of the selective disease of certain structures of the cornu ammonis (Sommer's sector) under different pathologic conditions has frequently been discussed.[19] Spielmeyer [20] expressed the belief that vascular factors are responsible—a deficient blood supply of this region. Vogt [21] assumed a certain vulnerability of the neurons and an affinity for certain toxins (*Pathoklise*). Examples supporting each theory or pointing to

20. Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:756, 1925.

21. Vogt, O.: Der Begriff der Pathoklise, J. f. Psychol. u. Neurol. **3**:245, 1925.

a combination of both factors may be cited. But the possibility should also be considered that elimination and distribution of toxic products may take place via not only the vascular system but the cerebrospinal fluid. Therefore, one would expect that structures which are closer to the ventricles and subarachnoid spaces are under the influence of higher concentrations of toxic substances dissolved in the cerebrospinal fluid. It has not been proved that insulin is eliminated into the cerebrospinal fluid, but this histologic study makes one think of such a possibility.

The manner in which hyperinsulinism produces damage to the brain is not known. Again, one may think of vascular factors—spasm of blood vessels during the seizures, stasis, thrombosis and hemorrhages. The histopathologic pictures which have been described do not lend themselves, however, to such an interpretation. One might, instead, assume a direct effect of the insulin on the neurons. It is known that insulin in large doses, producing hypoglycemic shock, interferes with the utilization of oxygen and dextrose by the gray matter of the brain, as was demonstrated in experiments on animals by Holmes [22] and in man by Dameshek, Myerson and Stephenson.[23] One might think, therefore, that "intracellular anoxemia" during the insulin shock may be responsible for the severe, generalized disease of the neurons following prolonged treatment with large doses of insulin, which has been described in this paper.

SUMMARY AND CONCLUSIONS

Injections of insulin into rabbits were followed by convulsive seizures after approximately two hours. The shock was interrupted by giving solutions of dextrose by stomach tube or intravenously. The average dose for the production of convulsive seizures was about 2.5 units per kilogram of weight. Sensitization to the effect of insulin occurred, but disappeared after about two weeks.

Injections of up to 70 units of insulin over different periods did not produce microscopically demonstrable damage to the brain. Injections of from 70 to 150 doses were followed by mild histopathologic changes, while doses of from 200 to 400 units injected over a period of two months severely damaged the cerebral neurons.

There was a difference between the histopathologic changes in the brains of rabbits which had died during a convulsive seizure and those of rabbits which were allowed to survive for several weeks or months. In the first group severe disease of the ganglion cells in the form of liquefaction, vacuolation and homogenization, was predominant. In the

22. Holmes, E. C.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

23. Dameshek, W. A.; Myerson, A., and Stephenson, C.: Insulin Hypoglycemia, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

second group the picture was characterized by marked shrinkage of the cytoplasm and nuclei. Diminution in the number of neurons in various cortical areas was observed in both groups to a more or less marked degree.

The pathologic changes seem to be the result of anoxemia—not anoxemia resulting from lack of oxygen following vascular disturbance but "intracellular anoxemia," i. e., inability to utilize oxygen in the presence of large doses of insulin.

ORGANIZATION OF MEMORY TRACES IN THE KORSAKOFF SYNDROME

LAURETTA BENDER, M.D.

FRANK J. CURRAN, M.D.

AND

PAUL SCHILDER, M.D.

NEW YORK

Karsten [1] studied psychic saturation by directing normal subjects to perform simple drawings, like fence pickets, and simple designs continuously until the subjects were completely exhausted and refused to go on. She found dissolution of the original configuration in the course of such an experiment. The drawing became disorderly and loosely connected, devoid of definite boundaries and broken up into little independent fragments, and the larger portions were disintegrated. Two of us (F. J. C. and P. S.) [2] who studied verbal material with a similar method, found evidence of organizing forces and active processes during repetition of the recall of a story told once to the patient. In cases of organic memory disturbances, the evidence of acceleration and exaggeration of organizing processes was striking.

A series of patients with Korsakoff's syndrome were examined during this investigation. One of us (L. B.) had collected a large mass of material concerning the copying of gestalt patterns, first used by Wertheimer under various conditions, and was able even to trace the development from early childhood of the ability to draw these gestalt figures. The following characteristics of visual motor patterns were found in cases of the Korsakoff syndrome associated with alcoholic and traumatic psychoses: [3] There is a correct grasp of the figure as a whole and its orientation on the background, with a tendency to some reversion to primitive responses and bizarre confabulations of parts of the figure without interference in the structure of the gestalt; there may also be perseverative tendencies due to major impulses.

From the department of psychiatry of the New York University College of Medicine and Bellevue Hospital, Psychiatric Division.

1. Karsten, Anitra: Psychische Sättigung, Psychol. Forsch. **10**:142, 1928.

2. Curran, Frank J., and Schilder, Paul: Experiments in Repetition and Recall, J. Genetic Psychol. **51**:163, 1937.

3. Bender, L.: (*a*) Gestalt Function in Visual Motor Patterns in Organic Disease of the Brain, Including Dementia Paralytica, Alcoholic Psychoses, Traumatic Psychoses and Acute Confusional States, Arch. Neurol. & Psychiat. **33**:300 (Feb.) 1935; (*b*) A Visual Motor Gestalt Test and Its Clinical Use, to be published.

In the aforementioned investigations it had also been shown that there are forces in the memory of normal persons which tend to accentuate gestalt principles. A gestalt pattern drawn the day after exposure showed, for example, separation of two parts which either touched or crossed each other or completion of incomplete figures.

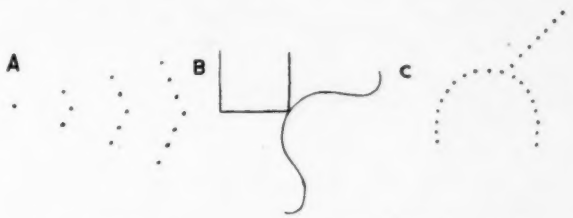

Fig. 1.—Gestalt patterns used in the investigation.

Fig. 2.—Repetitive copying of the gestalt pattern in figure 1 *A*.

We decided, therefore, to study the forces of organization in perception and memory in cases of the Korsakoff syndrome by using the method of repetition in copying gestalt patterns. Seven cases were used for this investigation. For the most part we used three patterns employed in the work of one of us (L. B.)—figures 3, 4 and 5,[3a] which are here labeled figure 1 *A, B* and *C*. When the patients were requested

to draw the patterns in figure 1 over and over again, the following changes took place:

1. In the first copy of the patterns in figure 1 *A*, dots might be replaced by crosses, circles and numbers, as described by one of us (L. B.). During the repetitions these changes might become progressively outspoken; instead of points there might finally emerge primitive vortexes of almost ½ inch (1.27 cm.) diameter. Figure 2 shows these developments (copies 1, 3, 8 and 23 are reproduced). The patient had before him, after the first copy, only his own immediately preceding attempt.

In the course of this development there was not only a change in orientation but complete reorganization of the pattern. However, it may be seen that the whole development had an inner logic.

2. In another case the points were immediately replaced by small ellipses and circles, but in the further development a dot was again put in the middle of each circle (fig. 3).

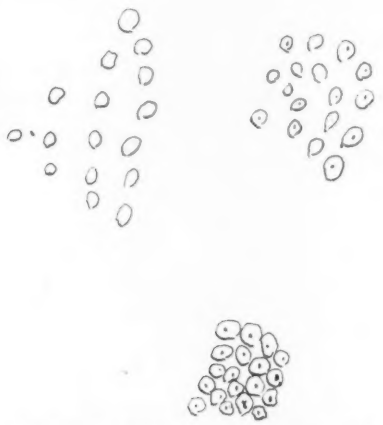

Fig. 3.—Repetitive copying of the gestalt pattern in figure 1 *A* in another case than that illustrated in figure 2.

The gestalt principle of this figure (fig. 1 *A*), which consists of three parallel, angular lines, was preserved in so far as the angular lines were retained as units; they tended, however, to become straight lines, and finally the straight line was replaced by a curve. This development took place even when the patient saw his previous performances.

Further changes in the series showed a marked tendency to contract the figure, and the patient now tended to link his small circles so that the whole ground was filled. This tendency to contraction to fill the space became progressively more marked. The result is the same whether the previous drawings of the patient are hidden from him or not, but the development is hastened when the patient has to depend entirely on memory. It is important that the inner pull is experienced subjectively by the patient. The patient may ask in the course of this endeavor, "Do you want them changed or not?" The development can be seen in figure 3.

3. Similar observations were made concerning figure 1 *B*. In the first copy the curved position was simplified only a little. In the eleventh copy the rectangle

was elongated and the curve simplified. After the eleventh copy the patient turned the page and had no figure before him. In from the twelfth to the twenty-fourth copy the rectangle was closed and progressively elongated (fig. 4 *A*). One sees here three important principles: (*a*) simplification of curves, (*b*) horizontal elongation and (*c*) tendency to closure.

4. In another case the tendency to closure came gradually into appearance. It was at first incomplete and later became complete. The patient, realizing the inner pull of the figure, asked, "Shall I close it?"

In this case there was a decided tendency to flatten the curve. The tendency became progressively stronger from one repetition to another. At the same time the curve was separated from the open quadrangle, and, in addition, there was a progressive pull of the curved line to a position below the bases of the pattern. One may speak here of progressive dislocation. There was also a progressive tendency to mark the beginning and the end of the curve (figure 4 *B*, which reproduces the first copy).

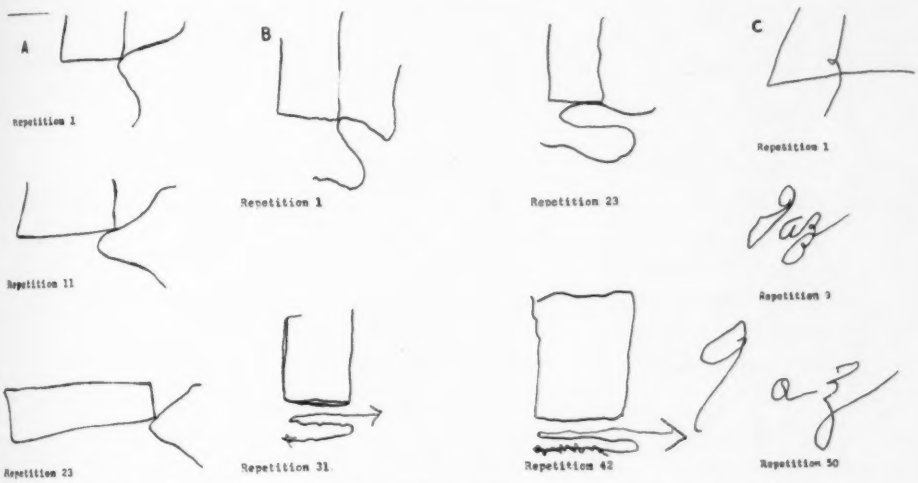

Fig. 4.—Repetitive copying of the gestalt pattern in figure 1 *B*, shown in three cases (*A*, *B*, and *C*).

5. In another case of the Korsakoff syndrome the gestalt of figure 1 *B* was disrupted completely, as figure 4 *C* shows. The curve with one vertical line of the quadrangle seemingly suggested to him a letter. This letter became definite only after the third repetition; then in the following repetitions he changed the gestalt completely into a word, as seen in the ninth repetition. In the next forty repetitions he retained this word, but separated it into single letters from about the fiftieth repetition on. When one gestalt principle was discarded, another was put in its place. The development of this new gestalt was gradual.

6. Another patient transformed the pattern of figure 1 *B* progressively into that of a staircase. A new organization was built up from parts of the previous organization.

7. It will be sufficient to give one instance of how figure 1 *C* may be progressively transformed into a new gestalt pattern, in which the more complicated

angular connection between the straight line and the circle was substituted after the twentieth repetition for a simpler ornamental design. In figure 5 it is obvious that forces of organization had come into play.

COMMENT

As one of us (L. B.) has shown, in Korsakoff's syndrome there is a tendency to substitute for the simple geometric units confabulations in the form of letters or numbers from the banal material of every day experience, as well as a tendency to go back to more primitive patterns. Our investigations with repetition of drawings show that even in the cases in which the first production does not show regression to the more primitive pattern, subsequent repetitions will reveal it. The circle, the vortex and the curve are form principles which dominate the gestalt

Fig. 5.—Repetitive copying of the gestalt pattern in figure 1 *C*.

drawings of children up to the ages of 4 and 5. The same may be said concerning the tendency to closures, filling the figure and separation of gestalten and the subsequent rigidity of the gestalt principles. Our experiments show further that one deals indeed with field forces and principles of organization. These field forces are obviously present from the beginning. They come into clear relief through repetitions. They are so strong that in some cases they force the patient to produce them even when he still has the original pattern before him, but they have a more decided effect on memory material. Experiments of this kind show decidedly that an attempt to understand an organic defect merely as a defect is futile. The person with an organic defect is seemingly more than normally at the mercy of field forces and tendencies to organization, which, as the experiments on representations

and memories of one of us (L. B.) have shown are also present in the normal person. These field forces tend to simplification and rigid organization of the field, until a stage is reached which has similarities to the processes of organization as they take place in the child of 4 or 5 years. Although the basic principles of organization are identical in the various cases studied here, variations exist: In one case the curve becomes merely more primitive; in the second it is more flattened, and in the third it becomes transformed into a letter. The action of the field forces is, therefore, determined not merely by the characteristics of the figure as such but by individual attitudes. It is important that when a field force has once made its appearance it acts with great consequence through the whole series of pictures produced. The organic disease not merely destroys but allows the liberation or emergence of forces which are otherwise kept in check. One cannot understand the psychology of the Korsakoff syndrome if one considers merely the obvious difficulty in retention of memory. One deals not merely with the fading of traces but with a new type of organization of the traces. Two of us (F. J. C. and P. S.) have come to similar conclusions, on the basis of studies with verbal material.

From a practical point of view we have found this method useful in the differentiation of organic and psychogenic disturbances in memory.

SUMMARY

In seven cases of the Korsakoff syndrome the patients were requested to draw a gestalt pattern repeatedy. In such a series of repetitions, instead of the perceived dots there may be produced crosses, circles, numbers and vortexes. Patterns not only are changed in orientation on the background but may be completely reorganized. The tendency to curves instead of angles may come into appearance. Figures may be contracted or expanded and elongated, especially in the horizontal plane. Curves may be simplified, flattened or reorganized into staircase patterns. The tendency to closure may become increasingly obvious. Parts of the figures may be progressively dislocated. Adjoining configurations may be completely separated from each other. These changes take place in perceptive as well as in memory patterns and represent reversion to a primitive type of organization in the perceptive field. They are the expression of strong field forces which have been liberated by the organic process. The psychology of the Korsakoff syndrome cannot be understood merely from the point of view of the fading of memory traces. There is a different type of organization comparable with organizations in childhood and, under special conditions, in the normal person.

VARIABILITY OF CIRCULATION TIME IN NORMAL AND IN SCHIZOPHRENIC SUBJECTS

H. FREEMAN, M.D.
WORCESTER, MASS.

In a previous investigation of the circulation time in normal and in schizophrenic subjects [1] it was found that the psychotic group was characterized by abnormal slowing of the rate of blood flow. In a comparison of determinations made under basal and those made under nonbasal conditions on the same day, the schizophrenic patients showed less consistency between the two readings than the nonpsychotic subjects. As the conditions involving nonbasality may vary considerably among different persons, this conclusion must be stated with a certain degree of reservation. An investigation was planned, therefore, in which repeated determinations of the circulation time would be made solely under basal conditions in both groups of subjects, with the object of determining whether in this function, as in many others, the schizophrenic organism would evidence its characteristic variability.[2]

In the present study two determinations of the circulation time, with other physiologic processes, were made at intervals of four weeks on twenty-nine normal men and thirty-two men suffering from schizophrenia but otherwise without disease. During this interval both groups of subjects lived in the same ward, ate approximately the same food and went through a similar amount of activity. Thus, the environmental conditions for the two types of subjects were essentially equal and were unchanged over the interval.

METHOD

The technic of the test may be described briefly. The subject rests for thirty minutes in bed, after abstinence from food for fourteen hours. The blood pressure and pulse rate are taken. A small intradermal wheal of a 2 per cent solution of procaine hydrochloride is made over the median basilic vein, in order that the pain of the subsequent venipuncture may be abolished and any concomitant circulatory changes thus avoided. A tourniquet is placed on the arm, and through

From the Research Service of the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research.

1. Freeman, H.: The Arm-to-Carotid Circulation Time in Normal and Schizophrenia Subjects, Psychiatric Quart. **8**:290, 1934.

2. Hoskins, R. G., and others: A Cooperative Research in Schizophrenia, Arch. Neurol. & Psychiat. **30**:388 (Aug.) 1933.

the anesthetized area a needle is inserted into the vein. The tourniquet is then released, and after an interval of sixty seconds, to allow the effects of venostasis to disappear,[3] 0.5 cc. of a 2 per cent solution of sodium cyanide (10 mg.) is discharged suddenly into the vein. The arrival of the cyanide at the carotid sinus is marked by rapid onset of dyspnea, and the interval between this phenomenon and the beginning of introduction of the solution, as measured by a stop watch, is taken as the arm to carotid circulation time. If the end-point is not sharp or is unusually delayed, the test is repeated after ten minutes, the amount of cyanide being increased by 2 mg. until an adequate response is evoked.

RESULTS

The data on circulatory and metabolic processes derived from the tests are presented in tables 1 and 2. From the values in these tables, it is apparent that the physiologic status of neither the group of normal subjects serving as controls nor the group of patients changed significantly between the determinations. There are, however, differences between the patients and the normal subjects. The circulation time for the patients is significantly longer, thus confirming the results of the previous investigation.[4] Systolic and diastolic blood pressures, as well as basal metabolic rates, are significantly lower in the schizophrenic subjects, but no significant difference is found between the pulse rates for the two groups.

The variability in the readings of the circulation time has been determined both for the individual and for the group. These measures of variation are given in table 1 in terms of standard deviations, so as to present them in actual time units. The intra-individual values are 5.6 seconds for the patients and 3.7 seconds for the normal subjects. This implies that, on the average, a normal person might deviate in his circulation time no more than 3.7 seconds in either direction from his theoretical mean value during approximately two thirds of the time, while the schizophrenic patient might vary on the average up to 5.6 seconds from his mean. The interindividual values are 7.5 seconds for the patients and 4.9 seconds for the subjects used as controls. It is

3. Looney, J. M., and Childs, H.: A Comparison of the Methods for the Collection of Blood to Be Used in the Determination of Gases, J. Biol. Chem. **104**:53, 1934.

4. In the present investigation, the mean values for the circulation time for both the patients (23.7 seconds) and the normal subjects used as controls (18.7 seconds) are significantly different from those obtained in the previous study,[1] in which the mean time for the patients was 26.7 seconds and that for the normal subjects 21.9 seconds. These differences may be attributed to three factors: First, in the present series tests in which values were abnormally high were all repeated, and results which could not be confirmed were discarded; second, the normal subjects and patients of the present series were younger and less sophisticated in test procedures, and third, the present group of patients was in a more acute stage of the psychosis.

TABLE 1.—*Determinations of Circulation Time Expressed in Seconds Made at Intervals of One Month*

	Patients			Normal Subjects	
Patient No.	First Determination, Sec.	Second Determination, Sec.	Control No.	First Determination, Sec.	Second Determination, Sec.
1	29.3	36.9	1	16.0	18.3
2	22.2	28.7	2	18.3	15.6
3	27.4	21.0	3	28.2	18.2
4	19.6	22.2	4	15.6	28.0
5	24.4	37.6	5	14.1	11.0
6	25.2	21.0	6	12.0	20.4
7	20.0	19.3	7	22.7	20.9
8	17.0	18.0	8	17.0	17.2
9	24.0	22.0	9	20.0	15.0
10	25.0	23.0	10	20.8	16.6
11	27.0	24.6	11	14.0	17.6
12	27.2	22.6	12	14.0	13.0
13	30.0	24.0	13	24.4	18.0
14	17.6	17.1	14	16.2	18.2
15	26.0	15.0	15	23.8	26.4
16	19.5	25.4	16	24.1	17.8
17	27.0	25.0	17	18.2	17.6
18	31.0	36.0	18	20.0	20.0
19	17.0	23.4	19	21.8	14.6
20	16.7	19.4	20	17.8	26.0
21	35.0	28.6	21	15.2	12.4
22	15.4	35.0	22	13.5	12.1
23	32.1	22.8	23	21.0	22.4
24	17.0	20.0	24	18.0	16.8
25	17.0	27.0	25	16.6	21.6
26	25.5	26.4	26	22.0	23.0
27	20.6	12.0	27	26.0	25.0
28	14.0	12.6	28	25.2	15.2
29	30.0	21.0	29	18.0	12.6
30	18.0	15.0	..	....	....
31	22.1	46.0	..	....	....
32	21.0	21.2	..	....	....
Means (sec.)	23.2	24.1		19.1	18.3
Standard Deviations (sec.) — Within individual subjects	±5.6			±3.7	
Standard Deviations (sec.) — Between individual subjects	±7.5			±4.9	

TABLE 2.—*Means for Each of Two Determinations of Blood Pressure, Pulse Rate and Basal Metabolic Rate on Twenty-Nine Normal Subjects and Thirty-Two Schizophrenic Patients Made at Intervals of One Month*

		First Determination	Second Determination
Systolic blood pressure, mm. of mercury	Controls	112.1	111.1
	Patients	103.3	104.4
Diastolic blood pressure, mm. of mercury	Controls	70.3	71.3
	Patients	67.0	67.0
Pulse rate	Controls	64.4	61.6
	Patients	61.3	60.0
Basal metabolic rate (%)	Controls	93.0	89.2
	Patients	84.4	84.5

evident, therefore, that with respect to the circulation time schizophrenic persons, both within themselves and as a group, are significantly more variable than normal persons. That this increased variation should be found in such a fundamental physiologic function as the circulation time is additional evidence of the abnormal homeostasis characteristic of this psychosis.[2]

The data were further analyzed to determine whether any difference in variability existed between persons having high and those having low values for circulation time. The average value for each group was taken as the point of division. It is evident from table 3 that the intra-individual standard deviations are greater for the subjects having high values; i. e., their consistency on repeated determinations is less. Here, again, the normal subjects seem to have smaller intra-individual

TABLE 3.—*Interindividual and Intra-Individual Standard Deviations of Circulation Time for a Group with High and a Group with Low Values for this Variable, Based on Two Determinations Made One Month Apart on Twenty-Nine Normal Subjects and Thirty-Two Schizophrenic Patients*

		Patients, Sec.	Normal Controls, Sec.
Within individual subjects.....	High.....	±7.0	±4.6
	Low.....	±3.7	±2.8
Between individual subjects.....	High.....	±5.0	±2.6
	Low.....	±3.9	±2.8

standard deviations than the patients in their respective divisions, which confirms the previous findings relative to their greater consistency. Whether the greater degree of variability in persons having a longer circulation time is inherent in their circulatory status or is due to technical error is difficult to decide. If a dose below that necessary to produce an adequate stimulus to the respiratory center is administered, the value for the circulation time may be unduly increased. This is more likely to occur in persons having a long circulation time, since they require, in general, somewhat greater doses than those having a short circulation time. In the present investigation, however, no determination was accepted as satisfactory unless the end-point (onset of dyspnea) was sharp. Repetitions with higher doses were always made promptly in cases of doubtful reactions. There is, however, a psychologic aspect to consider. Under the influence of emotion, such as apprehension of the test, the rate of blood flow is likely to become more rapid. From a purely physical standpoint, less variation may be

expected in persons having a short circulation time, since they are nearer the physiologic limit.

In this connection may be discussed the value of measurement of circulation time as a clinical constant applicable to the individual person. The interindividual standard deviations given in table 2 are significantly greater than the intra-individual standard deviations. This implies that the individual is more homogeneous than the group with respect to circulation time. However, when the samples are subdivided into groups characterized by high or low circulation time, the interindividual standard deviations are not significantly larger than the corresponding intra-individual values for either patients or normal subjects used as controls, as may be seen in table 3. This implies that persons within a given group, i. e., with either a high or low circulation time, do not differ significantly from each other. It would seem that although the individual may be more consistent than the group, his consistency is limited to his identification as having either a high or a low circulation time, and to this extent alone can circulation time be considered as a clinical constant.

In an attempt to determine the factors having an influence on the circulation time, correlation coefficients for this function versus other physiologic variables were determined for the group as a whole. The coefficients for circulation time versus blood pressure, age, basal metabolic rate, weight, surface area and blood volume were not significantly different from zero. For the pulse rate, however, the interindividual correlation coefficients were —0.56 for the patients and —0.10 for the normal subjects. The difference between these correlation coefficients is statistically significant. The negative nature of the relationship, i. e., the lower the pulse rate the longer the circulation time, is what one would expect from a mechanical point of view. The more intimate relationship between these two factors in the schizophrenic group adds further weight to the hypothesis of Hopkins and Jellinek that in this psychosis the hydrostatic forces of the circulatory processes are less modified by neurogenic factors, owing possibly to diminution in the activity of the sympathetic nervous system.[5]

SUMMARY

In twenty-nine normal men and thirty-two men with schizophrenia who were otherwise healthy, the arm to carotid circulation time was determined under basal conditions by means of the sodium cyanide

5. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Psychologic and Organic Concomitants, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1933.

technic on two occasions, at intervals of a month. The following results were obtained:

1. The mean circulation time of the schizophrenic patients was significantly longer than that of the normal subjects in both series of determinations.

2. The variability in measurements of the circulation time was greater for the schizophrenic subjects than for the normal subjects used as controls, both for the individual and for the group.

3. For this function the homogeneity of the individual is greater than that of the group. The variability of the function is such, however, that measurement of the circulation time for a given person can be considered to be a clinical characteristic for that subject only so far as it enables one to place him as having a low or a high value.

4. The only variable which, in these samples, appeared to be correlated with the circulation time is the pulse rate. This correlation was greater for the group of schizophrenic patients than for the group used as a control.

CONCLUSION

On the average, schizophrenic patients have an abnormally slow and a highly variable rate of blood flow.

SPONGIOBLASTOMA POLARE

A CLINICOPATHOLOGIC STUDY OF TWELVE CASES

DEAN H. ECHOLS, M.D.
ANN ARBOR, MICH.

The purpose of this paper is to report 12 cases of spongioblastoma polare,[1] to correlate them with those of other authors and to analyze them from the clinical and pathologic point of view. Cases of glioma of this type have been reported singly and in small groups under several names. Some of these series of cases have dealt with spongioblastoma of a limited region, such as the optic nerve or brain stem. Cushing's group of 32 cases is the only large series which dealt with spongioblastoma of the brain as a whole. The 12 tumors reported on in this paper constitute all the spongioblastomas which occurred in a series of 263 microscopically confirmed cerebral gliomas, obtained at operation or necropsy at the University Hospital between July 1, 1930, and July 1, 1935. In 8 cases the tumor was in the posterior fossa of the skull; in 3, in the optic nerves or chiasm, and in 1 in the cerebral hemisphere.

REPORT OF CASES

CASE 1.—*Onset of symptoms ten weeks before death. No operation. Spongioblastoma of the pons, medulla and cerebellum.*

History.—George B., aged 16 years, had fatigue, headache, blurring of vision and vomiting five weeks before admission, on July 30, 1931. The later symptoms included fever, weakness of the right side of the face, staggering, dysphagia, diminished hearing and impaired taste.

Examination.—There were incomplete bitemporal hemianopia, nystagmus, limitation of lateral rotation of the eyes, peripheral palsy of the seventh nerve on the right, deviation of the palate to the left and staggering gait. Taste, hearing and swallowing were impaired. The tendon reflexes were normal. Sensory examination was unsatisfactory. There was no papilledema. The spinal fluid contained a trace of globulin and 9 lymphocytes per cubic millimeter; the pressure was normal. Roentgenograms showed that the skull was normal.

Course.—A diagnosis of hemorrhagic encephalitis was made. Although the possibility of tumor of the brain stem was realized, operation was considered inadvisable. Papilledema did not develop. The bulbar symptoms progressed until death, during the fifth week of hospitalization.

From the Laboratory of the State Psychopathic Hospital and the Division of Neurosurgery, the University of Michigan Medical School.

1. The histologic diagnoses in the 12 cases were verified by Dr. Percival Bailey.

Necropsy.—The pons and medulla were twice the normal size, the enlargement being slightly greater on the right side (fig. 1). The internal landmarks were partially obliterated by hard, whitish tumor tissue. The growth extended into both cerebellar hemispheres but not into the spinal cord or cerebral peduncles. There was no hydrocephalus.

Microscopic Description.—The tumor consisted of small unipolar spongioblasts, which grew between the preserved fiber tracts. Scattered neurons survived. The tumor cells did not produce a definite structure, and there was no distinct interlacing of the cell processes. There was moderate edema. The vascular system was not proliferated.

The tremendous enlargement of the brain stem and the brief duration of the symptoms are not incompatible when the structure of the

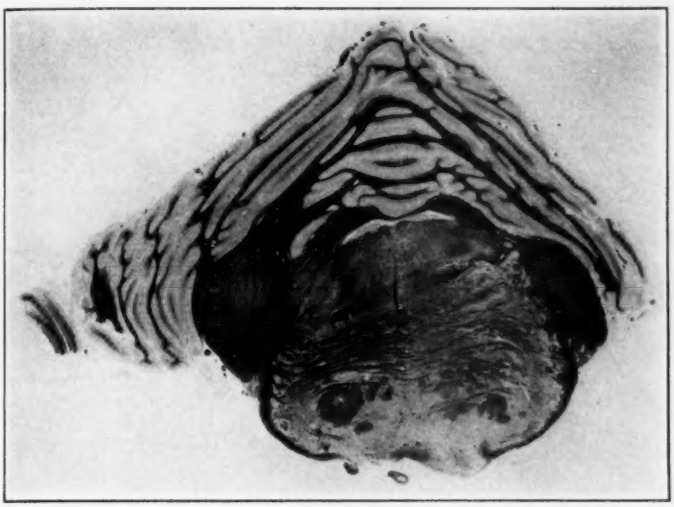

Fig. 1 (case 1).—Coronal section showing diffuse enlargement and demyelinization of the pons. Weigert-Kulschitzky stain; actual size.

spongioblastoma is understood. The elongated tumor cells grow between the fiber tracts and do not disturb their function until late.

CASE 2.—*Onset of symptoms two months before admission. Erroneous clinical diagnosis of tumor of the acoustic nerve. Pontile spongioblastoma observed at operation. Necropsy.*

History.—Ruby H., aged 7 years, began to lose weight two months before her admission, on Oct. 24, 1932. The succeeding symptoms included diplopia, ringing in the left ear, progressive deafness on the left, dysphagia, dysarthria and unsteady gait.

Examination.—The child was poorly nourished and acutely ill, with neuroretinitis, bilateral palsy of the sixth nerve, deafness on the left and weakness of the left side of the palate and tongue. The Babinski and Chaddock signs were

present bilaterally. There was no definite sensory disturbance. Roentgenograms showed a slight increase in the prominence of the digital markings of the cranial vault.

The presence of an acoustic neuroma was suspected, although it seemed unlikely when the patient's age was considered.

Operation.—On October 31 Dr. Max Peet exposed a greatly enlarged pons, and the operation was terminated. Emphysema of the neck, axilla and mediastinum developed, and death occurred on the following day.

Necropsy.—The pons was approximately three times the normal size (4.5 by 6 cm.) and was symmetrical, pinkish gray and soft (fig. 2). The internal landmarks were practically obliterated. The tumor extended from the upper part of

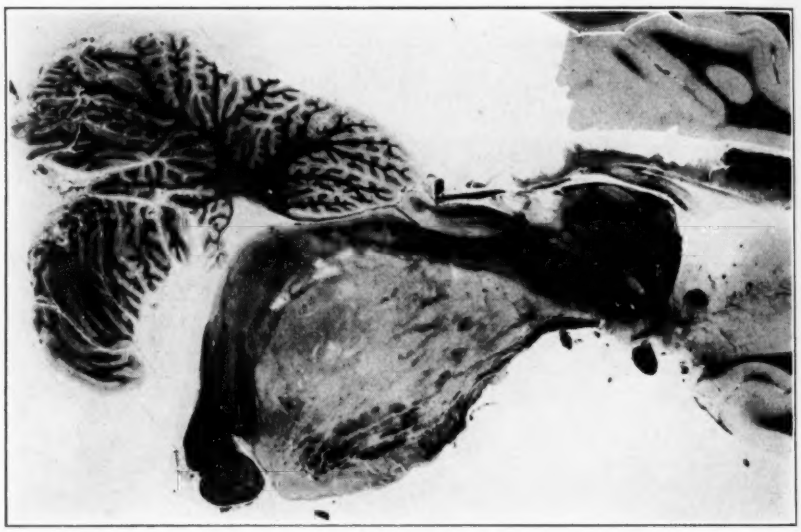

Fig. 2 (case 2).—Midsagittal section through the diffusely enlarged and greatly demyelinated pons. Weigert-Kulschitzky stain; actual size.

the medulla to the infundibular region and involved the left cerebral peduncle. The third ventricle was slightly dilated, but the aqueduct was patent.

Microscopic Description.—The tumor was formed of interlacing bands of spongioblasts, mostly unipolar, which were dissociated by edema. The long cell processes stained deeply in phosphotungstic acid-hematoxylin and azan preparations. There were no whorls or rosettes. Scattered neurons and nerve fibers were preserved. The connective tissue was limited to the walls of blood vessels.

In four cases in this series (1, 6, 9 and 10) in which no operation was performed, the tumor was in the brain stem. Occasionally, as in this case, exploration is indicated if there is a possibility that the symptoms of disturbance in the brain stem are produced by compression from an adjacent tumor.

CASE 3.—*Exophthalmos and blindness on the left side for thirty months. Partial excision of a spongioblastoma of the optic nerve and chiasm. Patient living after forty-one months.*

History.—Ralph A.,[2] aged 6 years, was admitted on Feb. 18, 1933, because of increasing prominence and blindness of the left eye for thirty months. The only other symptoms were frontal headache and nervousness.

Examination.—There were exophthalmos, atrophy of the optic nerve and blindness on the left and slight divergent strabismus. On the right visual acuity was 6/9. Roentgenograms showed enlargement of the left optic foramen.

A diagnosis of glioma of the left optic nerve was made. Operation was postponed for two months, at the request of the parents.

Operation.—On April 25 Dr. Peet exposed and elevated the left frontal lobe; a fibrous fusiform tumor of the left optic nerve was encountered. The tumor, which extended into the orbit and involved also the chiasm, measured 1.5 cm. in diameter. After the roof of the orbit was removed, the tumor was observed to extend to within 0.5 cm. of the globe. The entire left optic nerve, half of the chiasm and part of the left optic tract were excised.

Course.—The patient made a good recovery, but for a period of four months frequent aspiration and spinal drainage were required because of proptosis and bulging of the osteoplastic flap. When last heard from, forty-one months later, he was well and attending school. A photograph showed that he was considerably overweight, suggesting involvement of the region of the third ventricle.

Microscopic Description.—The tumor consisted of well preserved unipolar and bipolar spongioblasts (fig. 3). Their nuclei were round or oval and contained one or several nucleoli and numerous chromatin granules. The cell processes were long and stained deeply. Many of the cells ran parallel to the axis of the nerve, but others formed whorls or were condensed along the neurilemmal sheaths. There was moderate proliferation of the nerve sheaths and the adventitia of the blood vessels.

A preoperative diagnosis of spongioblastoma can be made with considerable certainty in case of a primary tumor of the optic nerve or chiasm occurring in a child.

CASE 4.—*Failing vision in the left eye for six years. Bitemporal hemianopia. Partial removal of a spongioblastoma involving the left optic nerve, chiasm and floor of the third ventricle. Necropsy.*

History.—William J., aged 15 years, was admitted on April 20, 1933, complaining of failing vision in the left eye, which was first noted six years before. For the last two years there had been frequent vomiting and headache. Partial ptosis of the left eyelid had been present for one year.

Examination.—There were atrophy of both disks, especially marked on the left, and bitemporal hemianopia, with islands of retained vision. The patient could read with the right eye but not with the left. The only other findings were vertical nystagmus and partial ptosis of the left eyelid. Roentgenograms showed erosion of the sella turcica of the type seen in intracranial hypertension and increase in the digital markings of the cranial vault. Films of the optic foramina were not taken.

A diagnosis of glioma of the optic chiasm was made.

2. This case, as well as cases 4 and 11, were the subject of a previous communication from this clinic (Mehney, G. H.: Primary Tumor of the Optic Nerve, Arch. Ophth. **16**:95 [July] 1936).

Operation.—On April 21 the left frontal lobe and part of the parietal lobe were exposed by Dr. Peet. When the frontal lobe was elevated, a tumor of the left optic nerve and the chiasm was observed to extend forward to within 2 mm. of the optic foramen and backward to the third ventricle. The left third nerve had been displaced laterally. Part of the tumor was removed without opening the third ventricle or cutting the right optic nerve. Hyperthermia and shock developed, and the patient died the next day.

Necropsy.—There was a defect in the floor of the slightly enlarged third ventricle. The edges of the opening contained necrotic, blood-stained tumor tissue. The growth involved the median and basilar surface of the frontal lobes and

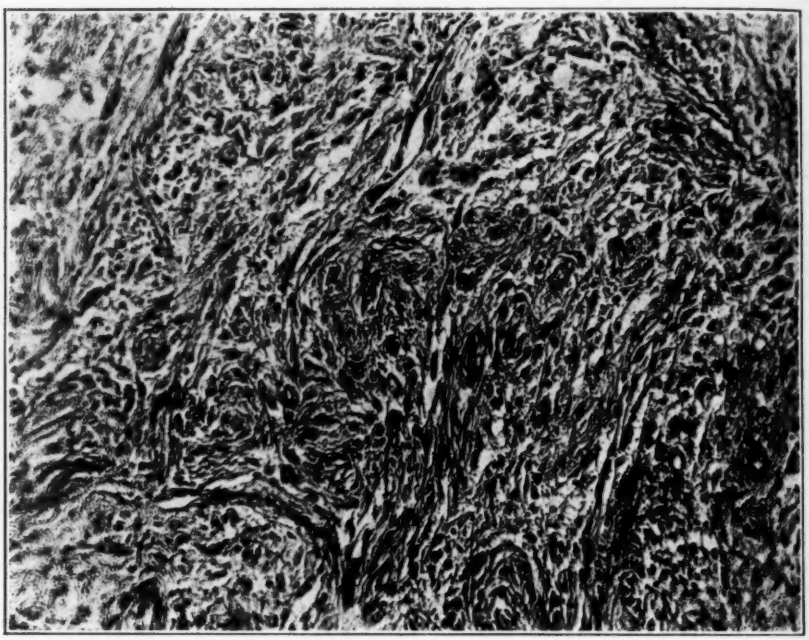

Fig. 3 (case 3).—Photomicrograph of a transverse section through the optic nerve, showing streams of elongated tumor cells. Mallory's acid-hematoxylin stain; Zeiss planar lens, 50 mm.

meninges. There were small areas of necrosis in the cortex of both frontal lobes and the right occipital lobe.

Microscopic Description.—The left optic nerve measured 1.5 cm. at its greatest diameter. The nerve and fragment of the chiasm were almost entirely replaced by tumor cells, but a few swollen, fragmented nerve fibers remained. The bulk of the tumor consisted of wavy bands of closely packed parallel cells, which had a process at one end. The appearance under low magnification was that of a fibroblastoma. Most of the cells were poorly preserved. Their nuclei were pyknotic and fragmented. There were numerous areas of edema and necrosis. The connective tissue was limited to the blood vessels and nerve sheaths.

The correct preoperative diagnosis of spongioblastoma polare was also possible in this case. Death from hyperthermia following operation is an ever present danger in surgical procedures involving the optic nerve.

CASE 5.—*Syndrome of involvement of the cerebellopontile angle for one year. Excision of a spongioblastoma of the eighth nerve. Death on the fifteenth day after operation. Necropsy.*

History.—Louise P., aged 60 years, was admitted on Sept. 5, 1933, complaining of nausea, diplopia, deafness on the right, vertigo and staggering to the right. The first symptom, tinnitus on the right, appeared one year before admission and was followed by deafness, twitching of the right side of the face and, finally, facial palsy.

Examination.—The objective findings were peripheral choroiditis on the left, concentric contraction of the form field of the left eye, bilateral contraction of the color fields, horizontal nystagmus when looking to either side, vertical nystagmus when looking upward, hypesthesia of the right side of the face, peripheral facial palsy and nerve deafness on the right, weakness of the right side of the palate, unsteady gait and a tendency to fall to the right. Roentgenograms showed that the skull was normal.

A diagnosis of tumor of the acoustic nerve was made.

Operation.—On September 21 Dr. Peet exposed a tumor of the eighth nerve through a right suboccipital approach. The growth was soft, grayish and granular and had none of the characteristics of acoustic neuroma. It pressed on the fifth, seventh, ninth, tenth and eleventh nerves and indented the pons and medulla. All the tumor was removed. Death from pneumonia occurred on the fifteenth day after operation.

Necropsy.—There was an area of superficially destroyed brain tissue, the size of a fifty cent piece, at the right cerebellopontile angle. Sections through the brain stem and cerebellum showed numerous small hemorrhages. The tumor had been completely removed at operation. There was no hydrocephalus.

Microscopic Description.—The eighth nerve was almost entirely replaced by unipolar and bipolar spongioblasts, the long, wavy processes of which extended in various directions, producing, at first glance, the appearance of a fibroblastoma. Whorls of cells were present. In a few places the spongioblasts were concentrated around blood vessels, forming pseudorosettes. The cell processes were not attached to the walls of vessels. In a few areas the network of cells was loose, and the nuclei were pyknotic or fragmented. There were occasional giant spongioblasts with one or several nuclei. Connective tissue was scarce, except in the proliferated nerve sheath. There was practically no fat.

This is the only case reported, as far as I know, of spongioblastoma of the acoustic nerve. The sections were stained by a variety of methods, and the several neuropathologists who studied the tumor have agreed that it could not be an acoustic neuroma. However, this case again brings up the question of the relationship between glioma of the brain and neuroma of the peripheral nerves. It is assumed that the glioma in this case originated in the central part of the acoustic nerve,

rather than in the peripheral portion, which is the site of origin of the neuroma. The fact that the internal acoustic meatus was not enlarged supports this assumption.

CASE 6.—*Vague symptoms for eight months followed by hemiparesis and, finally, bulbar palsy. Patient moribund on admission. Spongioblastoma of the medulla seen at necropsy.*

History.—M. Y., aged 9 years, entered the hospital in a critical condition, on Nov. 17, 1933. She had been "weak and run down" for eight months. During the last two months there had developed partial paralysis of the left arm and leg, which was attributed to poliomyelitis. Five days prior to admission dysphagia, hoarseness, vomiting and coughing developed.

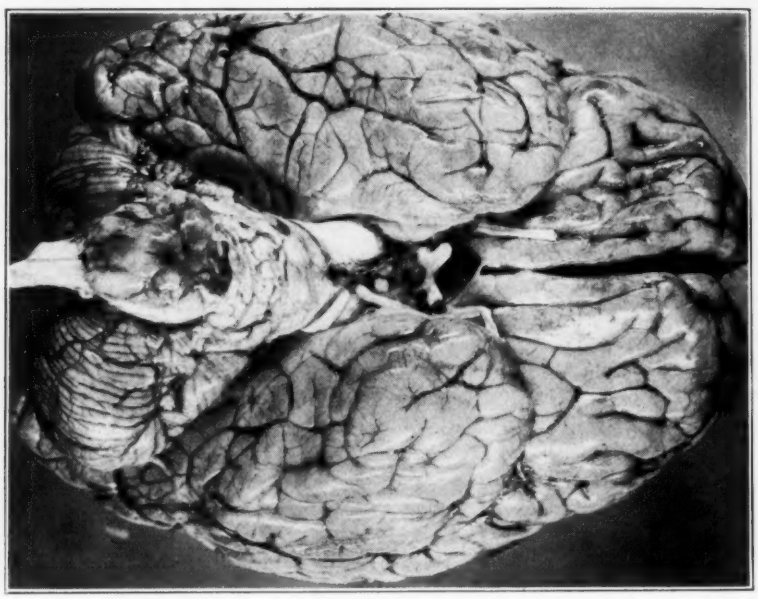

Fig. 4 (case 6).—Nodular tumor of the medulla.

Course.—A neurologic examination was not made. The child was treated for pneumonia and possible streptococcic laryngitis in the ward for contagious diseases. Death, on the fifth day, was due to bulbar paralysis.

Necropsy.—The medulla was greatly enlarged, its diameters measuring 4 and 5 cm. (fig. 4). In the region of the olives the surface was studded with small, soft, reddish gray nodules. Sections through the medulla revealed partially necrotic tumor tissue. There was no invasion of the pons and no hydrocephalus.

Microscopic Description.—The tumor was composed of closely packed, interlacing bundles of unipolar and bipolar spongioblasts. At the periphery of the tumor the uninvaded fiber tracts were compressed, giving the appearance of sharp demarcation. In some parts of the tumor there were numerous small cysts and areas of necrosis. Occasional calcified blood vessels were seen. Connective tissue was observed only in the walls of vessels.

High voltage roentgen therapy is generally thought to be beneficial in treatment of glioma of the brain stem. This patient's life might have been prolonged by such treatment had the diagnosis been made early in the course of the disease.

CASE 7.—*Failing vision for two years; headache, vomiting and ataxia for two months. Removal of a spongioblastoma of the left cerebellar hemisphere and fourth ventricle. Irradiation. Patient living after thirty months.*

History.—Minta F., aged 10 years, had noticed progressive loss of vision for two years. Two months preceding her admission, on Feb. 20, 1934, there developed severe frontal headaches, projectile vomiting and ataxia of the left hand.

Examination.—Vision was limited to ability to count fingers. The optic disks were atrophic and were elevated 2 diopters. There was horizontal nystagmus on rotation of the eyes to the right. Movements of the left arm were ataxic. Ventriculograms showed dilatation of the lateral and third ventricles and the sylvian aqueduct. The fourth ventricle was flattened, apparently by pressure from below. Faint shadows of the calcium deposits were seen in the region of the left cerebellar hemisphere. The foramen magnum was enlarged.

Operation.—At operation, performed by Dr. Peet on Feb. 23, the left cerebellar hemisphere was observed to be almost entirely replaced by a soft, whitish tumor, which was excised. The growth, which nearly filled the fourth ventricle, was attached to its lining only at the floor. Most of the intraventricular neoplasm was removed by suction.

Course.—Convalescence was complicated by herpes zoster and otitis media. The patient was discharged on the thirty-second day following operation. She returned at intervals for roentgen therapy and, when last seen, thirty months later, had no complaints except ataxia of the left hand and blindness.

Microscopic Description.—The tumor consisted of irregularly shaped and poorly outlined cells, with foamy and degenerated cytoplasm. They contained one or several nuclei. There were areas of gliosis. The capillaries and small vessels were enlarged, and some of them had thickened walls. There were small deposits of calcium.

Unfortunately, all the tumor could not be removed because of its attachment to the floor of the fourth ventricle. One and a half years after operation there was no clinical evidence of recurrence, a result to be expected in an indolent tumor of this type.

CASE 8.—*Symptoms of increased intracranial pressure for ten weeks before operation. Suboccipital exploration revealed no tumor. Ventriculography. Removal of a spongioblastoma from the wall of a cyst in the right parietal lobe. Patient living after twenty-six months.*

History.—Mary A., aged 20, who was admitted on June 18, 1934, had had severe bitemporal headache nine weeks previously, after delivery of her first child. In addition, there were failing vision, buzzing in the ears, vomiting and attacks of weakness, dizziness and staggering.

Examination.—The patient was mentally clear but slow in speaking. The optic disks were elevated 4 diopters, and there were small hemorrhages in the retinas. The visual fields could not be tested. The pupils were large and equal, responding sluggishly to light. Lateral rotation of the eyes was limited and associated with

horizontal nystagmoid movements. The left knee jerk was more active than the right. The gait was unsteady, and there was a tendency to fall when the eyes were closed. There was slight dysmetria of the left hand. Figures traced on the left arm were not readily identified. Roentgenograms of the skull showed evidence of increased intracranial pressure.

Course.—On June 25 suboccipital exploration was performed by Dr. Edgar A. Kahn, but no tumor was observed. Immediately after closure injection of oxygen into the ventricles showed a tumor in the right parietal lobe. On the same day a cystic tumor was exposed and about 50 cc. of xanthochromic fluid removed. A mural nodule, the size of a golf ball, was completely excised. The patient made an uneventful recovery and was discharged on the fourteenth day after operation. When last heard from twenty-six months later, she was in excellent health and had a baby aged 2 months.

Microscopic Description.—The tumor was composed of unipolar and bipolar spongioblasts the long processes of which formed a loose network. In some places these processes were parallel and gave the appearance of schools of small fish. There were areas of necrosis, partially organized by connective tissue.

When a mural nodule is removed from a cystic spongioblastoma or astrocytoma, a permanent cure may result. It is noteworthy that this patient survived cerebellar exploration and parietal craniotomy, both of which were performed on the same day.

CASE 9.—*Symptoms for four months. Patient admitted while in coma; no operation; death twenty-eight hours later. Spongioblastoma of the pons, medulla and cerebellum observed at necropsy.*

History.—Roy M., aged 47, was admitted in coma on July 23, 1934. During the preceding four months he had been treated for sinusitis, pneumonia and empyema. Two months before admission there developed left facial paralysis and headache. Details of the illness were not obtained.

Examination.—The patient was comatose, emaciated, dyspneic, cyanotic and incontinent of urine. There was left facial paralysis and spastic right hemiparesis. The optic disks were not elevated. Roentgenograms of the chest and skull disclosed no pathologic changes.

Course.—The crossed paralysis and respiratory embarrassment indicated a pontile tumor; operation was not attempted. Death occurred twenty-eight hours after admission.

Necropsy.—A whitish tumor, the size of a peach, involved the left side of the pons and the cerebellopontile angle (fig. 5). The growth invaded the medulla, left brachium pontis, left flocculus and part of the lobulus quadrangularis anterior. The aqueduct was patent.

Microscopic Description.—The cerebellar part of the tumor had a fairly uniform appearance, being moderately cellular with scattered areas of necrosis. It consisted chiefly of spindle-shaped spongioblasts, which were arranged in bands and whorls. The cell processes were long and wavy and stained deeply. There were occasional astrocytes and multinucleated giant cells.

The pontile part of the tumor was less characteristic of spongioblastoma, being less differentiated and more cellular. Giant cells were more numerous.

CASE 10.—*Onset with syncope two months before admission. Left hemianesthesia, deafness on the right side and bilateral palsy of the abducens nerve. No operation. Spongioblastoma of the pons and medulla observed at necropsy.*

History.—C. K., aged 42, fainted while working in the sun two months before admission, on Sept. 17, 1934. Pain in the right temple, tinnitus and deafness on the right and left hemianesthesia developed several weeks later. For a short time he was unable to move the right eyeball or close the lid.

Examination.—The optic disks were normal. The pupils were unequal but reacted to light. There were bilateral palsy of the sixth nerve and horizontal nystagmus on attempted lateral rotation. The corneal reflex was absent on the right. Hearing was impaired, more so on the right; speech was bulbar in type. There were weakness, ataxia and anesthesia of the left side of the body. Roentgenograms showed that the skull was normal.

Fig. 5 (case 9).—Enlargement of the left side of the pons. Weigert-Kulschitzky stain; actual size.

Course.—It was thought that the patient had either an inoperable pontile tumor or encephalitis. The immediate cause of death, which occurred on the seventeenth day, was aspiration pneumonia.

Necropsy.—The medulla, pons and cerebellar peduncles were approximately twice the normal size (fig. 6). The right side of the pons was larger than the left; sections showed almost complete obliteration of the internal structures (fig. 7). Markings on the cerebellar hemispheres indicated that they had been forced into the foramen magnum. There was moderate internal hydrocephalus.

Microscopic Description.—Tumor cells were observed from the lower part of the right cerebral peduncle to the decussation of the pyramidal pathways. The tumor was compact and composed largely of unipolar spongioblasts. There were no mitoses. Many giant cells containing from three to six nuclei were present. Scattered through the tumor were preserved neurons and astrocytes. There was no connective tissue except in the walls of vessels.

In this case, as well as in cases 1, 2 and 9, there was not complete obstruction of the aqueduct, a characteristic feature of pontile glioma in most cases.

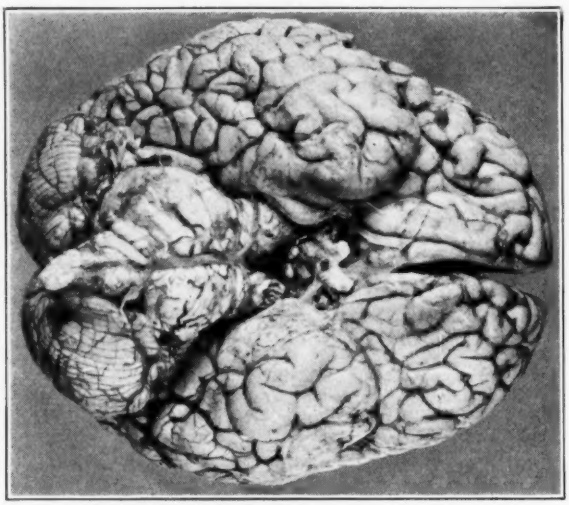

Fig. 6 (case 10).—Tumor involving the pons, upper part of the medulla and right cerebellar hemisphere.

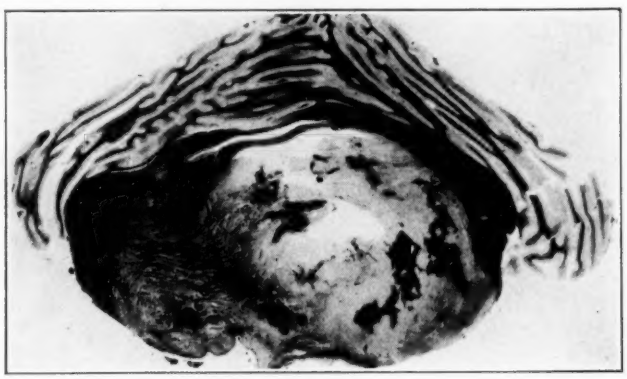

Fig. 7 (case 10).—Most of the pons is replaced by tumor. Weigert-Kulschitzky stain; actual size.

CASE 11.—*Unilateral exophthalmos and failing vision for eight weeks before operation. Removal of intra-orbital spongioblastoma of the optic nerve. Patient living after twenty-two months.*

History.—Clara M., aged 10 years, received a slight blow on the left eye five months before admission, on Nov. 13, 1934. Exophthalmos and failing vision on the left developed six weeks before admission.

Examination.—There were exophthalmos and papilledema of 4 diopters on the left. The blindspot was enlarged, and there was moderate contraction of the form field. Color vision was nearly lost. Roentgenograms showed a just perceptible increase in size of the left orbit and optic foramen.

Operation.—A diagnosis of spongioblastoma of the optic nerve was made. On November 24, through a left frontal approach, Dr. Peet exposed the optic nerves, which appeared normal. The roof of the orbit and optic foramen was removed, exposing a tumor, the size of a cherry, 3 mm. behind the eyeball. The nerve was sectioned close to the globe and near the chiasm, and the growth was removed intact.

Course.—Recovery was complicated by high fever, lasting eight days. The patient was discharged twenty-three days after operation. When last heard from, twenty-two months later, the child had no complaints except ptosis of the left eyelid.

Microscopic Description.—The tumor was composed of spongioblasts, mostly unipolar, which had invaded both the nerve and the nerve sheath. The long processes of the cells formed a dense network. There was extensive proliferation of the nerve sheath (fig. 8).

A permanent cure may have been obtained in this case.

CASE 12.—*Symptoms for three years. Obstruction of the cerebral aqueduct observed at operation. Spongioblastoma of the pons seen at necropsy.*

History—Maxine M., aged 17 years, was admitted on April 4, 1935, because of failing vision and staggering gait. There had been irritability and tiredness for three years. Intermittent diplopia and progressive loss of vision had begun two years before. The patient had staggered, especially to the right side, for eighteen months. Headache with vomiting had occurred at frequent intervals. Diminution in the sense of smell and intermittent incontinence of urine were late developments.

Examination.—There were partial loss of the sense of smell, atrophy of the optic disks, enlargement of the blindspots and concentric contraction of the visual fields. There was 1 diopter of papilledema bilaterally. Horizontal nystagmus was present on looking to either side. Weakness of the right side of the face was noted. The tendon reflexes were exaggerated on the right, and the abdominal reflexes were absent. There was a Hoffmann sign bilaterally, but no other pathologic reflexes. The patient staggered, especially to the right side. No definite sensory changes were observed. Roentgenograms showed separation of the cranial sutures, exaggeration of the digital markings, obliteration of the tuberculum sellae and clinoid processes and erosion of the base of the skull.

Operation.—Suboccipital craniotomy was performed by Dr. Peet on April 12. The fourth ventricle was exposed by an incision in the vermis. Dye injected into the lateral ventricle failed to appear in the fourth ventricle. A catheter could be inserted only 1 cm. into the aqueduct. The operation was terminated. The patient died of pneumonia five days later.

Necropsy.—A round, rubbery, bluish gray tumor, measuring 1 cm. in diameter, was observed in the dorsum of the pons, surrounding and occluding the aqueduct (fig. 9).

Microscopic Description.—The tumor consisted of elongated cells resembling spongioblasts. In some fields they were arranged in interlacing bands, but in others no definite arrangement was discernible.

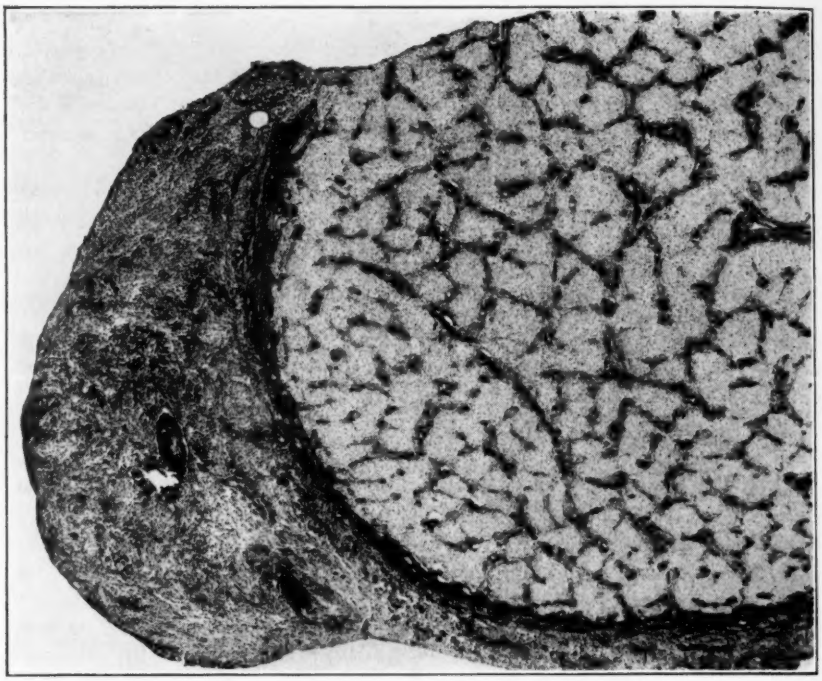

Fig. 8 (case 11).—Photomicrograph of transverse section through the optic nerve, showing infiltration of the nerve and its greatly thickened sheath. The diameter of the nerve is twice the normal measurement. Azan stain; Zeiss planar lens, 35 mm.

Fig. 9 (case 12).—The tumor completely surrounds the aqueduct. Weigert-Kulschitzky stain; actual size.

This case is an exception to the general rule that glioma of the pons does not occlude the aqueduct.

COMMENT

Survey of the Literature.—Spongioblastoma polare, also called spongioblastoma unipolare et bipolare or, simply, spongioblastoma, should not be confused with spongioblastoma multiforme, which is now generally called glioblastoma multiforme. Spongioblastoma polare was present in 3.7 per cent (32 cases) of the 862 cases of glioma in Cushing's [3] series, but less than 50 other cases are recorded in the literature under that name. Bailey and Eisenhardt [4] reported the 32 cases in Cushing's material. Pilcher [5] mentioned 22 cases, most of which were from Sachs' clinic, and described in detail the 11 tumors which were located in the pons. In Verhoeff's [6] 11 cases of spindle cell glioma of the optic nerve the tumor was undoubtedly spongioblastoma. Penfield [7] reported 6 cases. There are also a number of reports of single cases. The cases in which there were sufficient data are listed in the accompanying table and form the basis for the statistical figures used in this paper.

Many tumors reported under other names are thought to be identical with the spongioblastoma, including the group of *oligodendrocytomes à cellules fusiformes* reported by Roussy and Oberling.[8] The term "neurinoma centrale" used in the German literature by Josephy and others is considered to be synonymous with spongioblastoma.[8] Many of the variously named tumors of the optic nerve and chiasm belong also to this group, as do most of those in cases of "hypertrophy of the pons." A few of the other cases of probable spongioblastoma reported under other names are: the case of tumor of the optic nerve reported by Neame,[9] the 2 cases of glioma of the optic nerve associated with von Recklinghausen's disease reported by Goldstein and Wexler,[10] Weil's [11] case of "megalencephaly with diffuse glioblastomatosis of the

3. Cushing, H.: Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

4. Bailey, P., and Eisenhardt, L.: Spongioblastomas of the Brain, J. Comp. Neurol. **56**:391, 1932.

5. Pilcher, C.: Spongioblastoma Polare of the Pons, Arch. Neurol. & Psychiat. **32**:1210 (Dec.) 1934.

6. Verhoeff, F. H.: Primary Intraneural Tumors (Gliomas) of Optic Nerve, Arch. Ophth. **51**:120 (March) 1922.

7. Penfield, W.: Principles of Pathology of Neurosurgery, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, p. 303.

8. Bailey and Eisenhardt,[4] p. 392.

9. Neame, H.: Two Cases of Tumour of the Optic Nerve, Brit. J. Ophth. **7**:209, 1923.

10. Goldstein, I., and Wexler, D.: Spongioblastoma of Optic Nerve in Neurofibromatosis (Recklinghausen), Arch. Ophth. **7**:259 (Feb.) 1932.

11. Weil, A.: Megalencephaly with Diffuse Glioblastomatosis of the Brain Stem and Cerebellum, Arch. Neurol. & Psychiat. **30**:795 (Oct.) 1933.

brain" and the case of cellular glioma of the optic thalamus reported by Levison and Alter.[12]

Location and Gross Description.—Spongioblastoma polare frequently occurs along the cerebral axis, from the optic nerves to the medulla, but is seen also in other parts of the brain. In 31 per cent of all cases [13] the tumor occurred in the optic nerves and chiasm. Occasionally it extends as far as the optic disk and can be seen with the ophthalmoscope.[6] The chiasm is usually involved, but occasionally, as in case 11 of our series, the tumor is limited to the optic nerve.

Data in Cases of Spongioblastoma Polare Reported in the Literature

Author	Number of Cases	Average Age on Admission	Males	Females	Optic Nerves and Chiasm	Brain Stem	Cerebellum	Cerebral Hemisphere	Basal Ganglia	Third Ventricle	Eighth Nerve
Echols	12	21	5	7	3	6	1	1	..	..	1
Bailey and Eisenhardt [4]	32	20	15	17	9	5	7	6	3	2	..
Pilcher [5]	11	12	4	7	..	11	..	..	..	..	..
Verhoeff [6]	11	15.5	7	3	11	..	..	..	..	..	..
Penfield [7]	6	12	..	..	..	..	4	2	..	..	..
Cabot case 15482 (New England J. Med. **201**:1111 [Nov. 28] 1929)..	1	13	1	..	..	..	..	..	1	..	..
Hamby (Spongioblastoma Bipolare in Region of Hypothalamus Associated with Infantilism and Without Dwarfism, Arch. Neurol. & Psychiat. **31**:1258 [June] 1934)..	1	8	1	..	..	1	..	..	..	..	..
Sheldon, Parker and Kernohan (Occlusion of the Aqueduct of Sylvius, Arch. Neurol. & Psychiat. **23**:1183 [June] 1930).....	1	8	1	..	..	1	..	..	..	..	..
Hare and Wolf [14].....	1	8	..	1	..	1	..	..	..	..	..
Russell and Bland [17].....	2	13	1	1	1	..	1	..	..	..	..
Total number of cases.....	78	..	35	36	24	25	13	9	4	2	1

Involvement of the pons and medulla was reported in 32 per cent of all cases (table). The tumor may be limited to the pons but more often extends into the medulla or the cerebral or cerebellar peduncles, as in cases 1, 2, 9 and 10. The tumor may produce a nodular, a symmetrical or an asymmetrical enlargement. In cases 1, 2 and 10 the pons was from two to three times the normal size. In most cases reported in the literature under the term "hypertrophy of the pons" the tumor was undoubtedly a spongioblastoma, although in a few instances it may have been a diffuse astrocytoma.

12. Levison, L., and Alter, F.: A Case of Glioma of the Optic Thalamus, Am. J. Ophth. **6**:468, 1923.

13. The percentages used in this paper are based on the 78 cases listed in the table in which the diagnosis was certain.

The medulla is rarely involved alone, but this was true in case 6 of our series. The tumor reported by Hare and Wolf [14] involved the medulla and the upper two segments of the cord.

The cerebellum was the site of the tumor in 17 per cent of cases. In 11 per cent the growth occurred in the various lobes of the cerebrum, and in 5 per cent it arose in the basal ganglia. In the remaining 4 per cent of cases it occurred in miscellaneous locations.

Spongioblastoma polare is reddish gray, bluish gray or whitish. It may be either firm or soft. Rarely, the tumor is partially necrotic. Hemorrhage into the tumor is unusual. The spongioblastoma is never encapsulated, but degeneration is common. In the cerebellum and cerebrum the tumor may be predominantly cystic. In such cases there is usually a mural nodule. In case 8 the cyst contained 50 cc. of yellow fluid and a mural nodule the size of a golf ball. Deposits of calcium are uncommon and are rarely large enough to cast a shadow in roentgen films; the condition in case 7 and that in a case described by Bailey and Eisenhardt [4] are exceptions.

Microscopic Description.—The spongioblastoma polare is composed largely of varying proportions of cells resembling the unipolar and bipolar spongioblasts of the developing nervous system. They are pyriform or spindle shaped, with a long, thick process extending from one or both poles. The process of the spongioblast is long, being many times the length of the cell body, and is frequently wavy or corkscrew like. The process stains heavily, but neuroglia fibrils cannot be differentiated. The cytoplasm of the cell is scanty and either finely granular or homogeneous. The nucleus is oval, contains scattered chromatin and is usually placed in the center of the cell body. Mitotic figures and multinucleated cells are uncommon. Placed between the nucleus and the tail of the cell is a centrosome, with a clear halo.[15] Rarely, there is a diplosome or a triplosome. Bailey and Eisenhardt [16] stated:

> Some of the cells have small processes from various parts of the body so that they resemble astroblasts to a certain extent and in the spongioblastomas true astroblasts with sucker-feet on the vessel walls, and even minute astrocytes, may occasionally be found. But the vast majority of the cells are either unipolar or bipolar spongioblasts, as have been described.

The spongioblasts of the tumor are frequently grouped into bands with their long axes more or less parallel, resembling superficially a fibroblastoma. The cells grow along the nerve fibers without seriously

14. Hare, C., and Wolf, A.: Intramedullary Tumors of the Brain Stem, Arch. Neurol. & Psychiat. **32**:1230 (Dec.) 1934.

15. Bailey and Eisenhardt,[4] p. 423.

16. Bailey and Eisenhardt,[4] p. 424.

disturbing their function until late. Inclusions of astrocytes, astroblasts and nerve fibers complete the histologic picture.

The connective tissue is scant and usually limited to the walls of blood vessels. Various degenerative changes may be seen such as dissociation of the tumor cells by edema, cyst formation, hyaline transformation of cells and small deposits of calcium. Necrosis is uncommon. Intervascular degeneration occasionally leaves the cells in clumps around the blood vessels, giving the superficial appearance of an astroblastoma. However, careful examination shows that the cellular processes do not have end-plates on the walls of vessels, but simply curl around them.

Pilcher [5] subdivided his cases into three groups (primitive, pure and mature) to emphasize the fact that spongioblastoma is a transitional glioma lying histogenetically between the glioblastoma multiforme and the astrocytoma.

A new conception of the spongioblastoma has recently been advanced by Russell and Bland [17] as a result of their work with tissue cultures. They claimed that the spongioblastoma polare is a variety of astrocytoma and suggested that the term "piloid astrocytoma" is more suitable. (The term "piloid" was first used by Penfield [18] to describe the fusiform variety of fibrillary astrocyte which he observed in pathologic conditions entailing gliosis.) This interpretation, if correct, would explain the relatively slow clinical course which this tumor usually exhibits. Although this view is interesting, it needs further investigation.

Diagnosis.—The spongioblastoma polare has only a few clinical features which aid in its preoperative identification. Because of its indolence and manner of growth, the onset is often insidious and the course prolonged, the average duration of symptoms before operation being twenty-three months in Cushing's series and seventeen months in this series. This discrepancy is due to the fact that in the present series there was a higher percentage of spongioblastoma of the brain stem. This tumor usually occurs in children or young adults, the average in 78 cases being 17 years.

Spongioblastoma of the optic nerves, chiasm and tracts occurs almost exclusively in children, the average age in 24 cases being 10 years. Progressive loss of vision is the presenting symptom. Occasionally the tumor invades the optic disk and becomes visible with the ophthalmoscope. There may be exophthalmos. Roentgen films may show erosion of the anterior clinoid processes or enlargement of one

17. Russell, D. S., and Bland, J. O. W.: Further Notes on the Tissue Culture of Glioma with Special Reference to Bailey's Spongioblastoma, J. Path. & Bact. **39**:375, 1934.

18. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 455.

or both optic foramina. Spongioblastoma of the chiasm may be associated with obesity and other symptoms of disturbance of the hypothalamus when the latter has been pressed on or invaded. Craniopharyngioma and hypophysial adenoma may also give symptoms of involvement of the chiasm but have their own characteristic roentgenographic appearance, which permits a differential diagnosis. Meningioma producing similar disturbances by pressing on the optic nerves is rare in childhood. Spongioblastoma polare, like several other types of tumor of the brain, may be associated with von Recklinghausen's disease; 6 such cases have been reported.

Spongioblastoma of the cerebellum, cerebral hemisphere, thalamus and pons cannot be differentiated clinically from other gliomas.

Therapy.—Bailey [19] did not recommend surgical intervention in patients with spongioblastoma polare of the optic chiasm because of the danger of fatal hyperthermia. He found that these patients can be irradiated safely without preliminary decompression and with considerable benefit. Peet removes as much of the tumor as possible, leaving enough of the chiasm to retain nasal vision in one eye (cases 3 and 4). Surgical therapy is especially suitable in cases in which the tumor involves the optic nerve without affecting the chiasm (case 11).

Pontile and medullary spongioblastomas are inoperable, but exploration is indicated if the diagnosis of glioma is uncertain. Occasionally an operable tumor presses on the pons, leading to an erroneous diagnosis of pontile glioma. Roentgen irradiation, according to Bailey,[20] prolongs the lives of patients with the pontile variety of this tumor.

Spongioblastoma of the cerebellar and cerebral hemispheres can be completely excised in some cases.

Spongioblastoma of cranial nerves, except of the second, is rare. In case 5 the tumor arose from the acoustic nerve and was excised. The patient died of pneumonia two weeks later; necropsy revealed no remaining tumor tissue.

Prognosis.—Spongioblastoma polare is a slowly growing, relatively benign tumor. Unfortunately, it frequently occurs in the brain stem and other sites where operative removal is impossible. However, complete excision is occasionally possible when the tumor is located in the optic nerve or in the cerebellar or cerebral hemisphere.

Roentgen irradiation is believed to prolong the lives of patients with inoperable spongioblastoma of the optic chiasm or brain stem.

The average period of survival was twenty-six months in Cushing's group of 31 cases in which operation was performed, with 10 of the

19. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

20. Bailey, P.: Personal communication to the author, 1935.

patients living at the time the computation was made. Two of the patients were alive ten and eleven years, respectively, after operation. In Peet's group of 8 cases in which operation was performed, 4 patients (cases 3, 7, 8 and 11) were known to be alive forty-one, thirty, twenty-six and twenty-two months, respectively, after complete or partial excision of the tumor.

SUMMARY

Twelve cases of spongioblastoma polare of the brain are reported. They constitute 4.6 per cent of 263 cases of cerebral glioma in which histologic verification was made during a period of five years.

In approximately 80 per cent of all cases cerebral spongioblastoma occurs along the cerebral axis, from the optic nerves to the medulla.

Spongioblastoma of the optic nerves and chiasm can, as a rule, be recognized clinically. Spongioblastoma in other parts of the brain usually cannot be differentiated from other gliomas.

PSYCHOLOGIC STRUCTURE OF CATATONIA *

A PSYCHOPHARMACOLOGIC SURVEY UTILIZING SODIUM AMYTAL

MELVIN WILFRED THORNER, M.D.
PHILADELPHIA

In previous papers on the use of sodium amytal I [1] showed that this drug makes possible the eliciting of certain psychologic data not otherwise obtainable in some mental syndromes. In this paper it is my purpose to show what data have been secured in a study of the catatonic syndrome.

The material for this study represents a carefully selected group of patients showing catatonic manifestations of marked degree. The selection of a group on this basis may be expected to induce a quantitative error into the estimation of the results, but I considered that it would be best to avoid the induction of a qualitative error by the introduction of patients the diagnosis of whose condition might be questionable. Sixty-two patients were used, of whom some were followed for two years and none was observed for less than three months. This state hospital [2] material included both chronic and recently developed conditions. The analysis centered largely about four characteristic symptoms, although in each case an effort was made to visualize the reaction of the patient as a whole, in which setting the symptom occurred.

Since the catatonic state was described by Kahlbaum [3] in 1874 it has been the object of much interest and conjecture. Kraepelin [4] amplified the concept of this symptom complex and furnished a lucid picture of its outward manifestations. He gave the syndrome the position it now holds as a group under the heading of dementia praecox. He typified the condition as one of "stupor, negativism, automatism, muscular tension, excitement with stereotypy, verbigerations and echolalia, leading in most cases, with or without remissions, to a condition of mental

* From the Department of Neurology, Graduate School of Medicine, University of Pennsylvania.

1. Thorner, M. W.: (*a*) The Psycho-Pharmacology of Sodium Amytal, J. Nerv. & Ment. Dis. **81**:161, 1935; (*b*) The Psycho-Pharmacology of Sodium Amytal in Catatonia, ibid. **82**:299, 1935.

2. The patients were subjects in the Norristown State Hospital, Norristown, Pa.

3. Kahlbaum, K.: Die Katatonie oder das Spannungsirresein, in Klinisch Abhandlungen über psychische Krankheiten, Berlin, A. Hirschwald, 1874.

4. Kraepelin, E.: Lehrbuch der Psychiatrie, ed. 8, Leipzig, J. A. Barth, 1909-1913.

deterioration." To the last statement exception may perhaps be taken on the ground that it is too pessimistic and that many patients, particularly those with an acute onset, do not deteriorate. A second exception to Kraepelin's grouping may be made in that the symptoms of catatonia are not found invariably only in patients properly classed in the dementia praecox group. Thus, Strecker and Ebaugh [5] observed catatonic symptoms in twenty-five of one hundred and seventeen patients in whom a psychosis began after the age of 40.

Bleuler,[6] in discussing catatonia, hypothesized that schizophrenic negativism is dependent on four factors: ambivalence, ambitendency, splitting and imperfect logic. He stated further: "I have been unable to see a true motor disturbance in dementia praecox, either at the root of negativism or elsewhere."

From this brief discussion, it would seem that there has been a tendency to regard the group as unified symptomatically and, by inference, in an etiologic sense. This feeling has doubtless been intensified by the close similarity of the clinical pictures and surface manifestations of catatonic patients. Another apparent justification for this point of view is presented by pharmacologic reactions. De Jong,[7] Kaufman and Spiegel [8] and others have produced states resembling catalepsy in animals by injecting bulbocapnine. These states resemble superficially some catatonic phenomena seen clinically in human material and are reversed in both man and animals as far as surface phenomena are concerned by the action of sodium amytal.

Bleckwenn [9] expressed the belief that sodium amytal is "apparently a cortical depressant." Solomon and his associates [10] and others have agreed that sodium amytal arouses patients temporarily from catatonic stupor. In a previous paper I emphasized my conception that inhibition of higher cortical centers by sodium amytal is the probable mechanism by which the overinhibited catatonic patient is enabled to show the so-called release phenomena.

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5. Strecker, E. A., and Ebaugh, F. G.: Practical Clinical Psychiatry, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1931.

6. Bleuler, E.: Zur Theorie des schizophrenen Negativismus, Psychiat.-neurol. Wchnschr. **12**:171, 189 and 195, 1910-1911.

7. de Jong, M. H.: Démonstration du syndrome moteur catatonique chez le chat par injection de bulbocapnine, Presse méd. **36**:760 (June 16) 1928.

8. Kaufman, M. R., and Spiegel, E. A.: Experimentelle Analyse der Beeinflussung katatoner Zustände durch Einatmen von Kohlensäure-Sauerstoffmischungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **127**:312, 1930.

9. Bleckwenn, W. J.: The Use of Sodium Amytal in Catatonia, A. Research Nerv. & Ment. Dis., Proc. **10**:224, 1931.

10. Solomon, H. C.; Kaufman, M. R., and D'Elseaux, F.: Some Effects of the Inhalation of Carbon Dioxide and Oxygen, and of Intravenous Sodium Amytal on Certain Neuropsychiatric Conditions, Am. J. Psychiat. **10**:761, 1931.

This was considered as possibly analogous or related to release of the lower by the upper motor neuron of the corticospinal system. The last mentioned phenomenon was based on observations of the Babinski response and the increased knee jerk and ankle clonus in patients receiving an injection of sodium amytal. It was concluded further that minimal concentrations of sodium amytal may inhibit the activity of neurons concerned with the highest and phylogenetically latest developed functions. Increasing concentrations arrest the activity of successively lower layers of the neuronic network, and the phylogenetically oldest functions (largely of the autonomic nervous system) are the last to be affected.

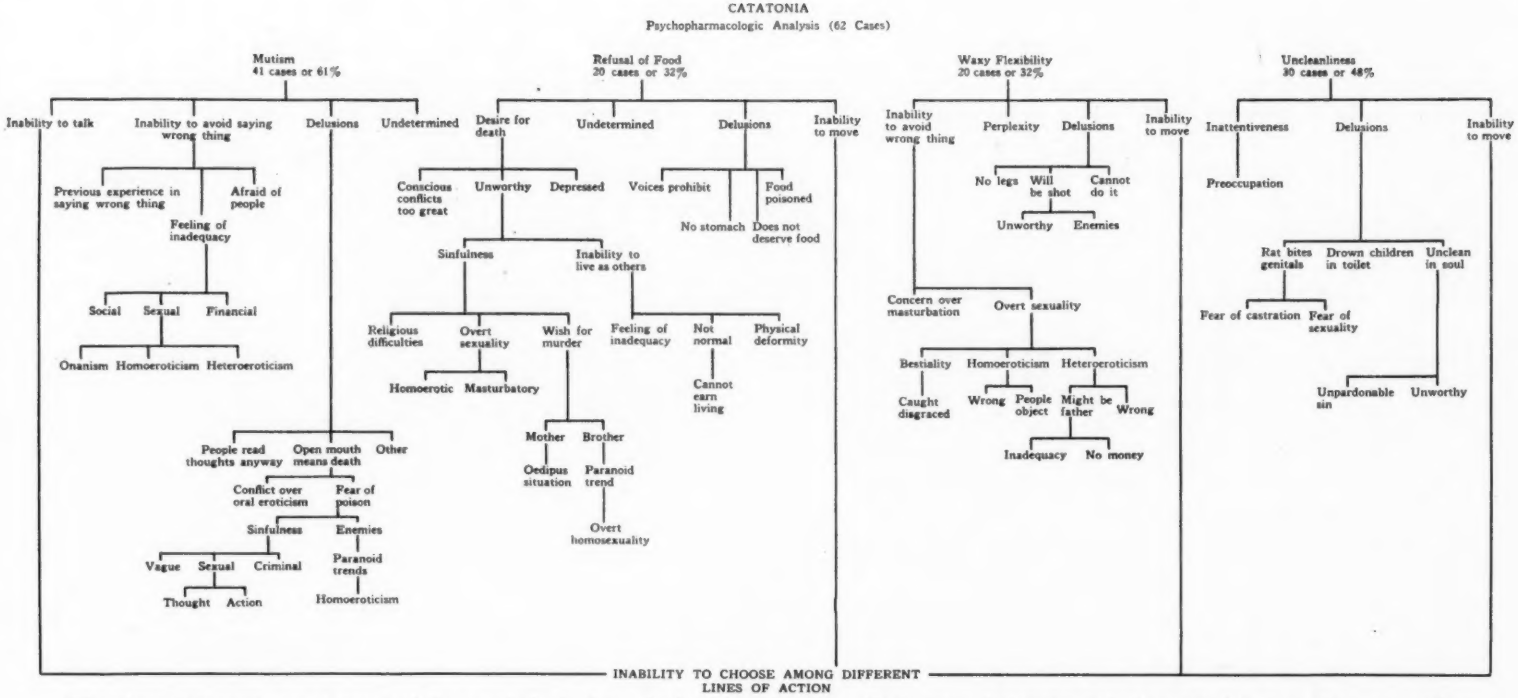
The preceding data, taken in their most optimistic sense, lead one to suspect that in the overinhibited catatonic patient it may be possible to examine the psychologic structure of the disease layer by layer in any given group. In this paper I shall endeavor to present the beginnings of such a study. Theoretically, one may judge more adequately of the validity of the hypothesis that these patients represent a group unified in the deeper structure of the psychologic state, as the surface manifestations suggest.

TECHNIC

The patients were placed in quiet surroundings, and intravenous injections of sodium amytal were made slowly. The patients were permitted to talk freely, but when they did not (which was infrequent), ambiguous questions were asked. At times word associations were used.

RESULTS

Mutism.—This symptom was noted in forty-one, or 66 per cent, of the patients studied. It ordinarily presents great obstacles to psychologic analysis of the psychotic reaction. Sodium amytal was given to each of the patients according to the method suggested in a previous paper.[1b] Briefly, the drug was given orally in ascending doses until psychologic effects were observed. When administration by mouth failed to produce the desired change in the psychotic reaction, the intravenous route, with small doses, was used. In this way, the underlying structures supporting the symptom were traced through successive layers by administration of varying concentrations (doses) of sodium amytal. In nine patients (22 per cent) the results were unsuccessful. The accompanying synthetic psychographic chart indicates superficially the findings obtained in the rest of the group. It will be noticed that under the subheading *Delusions* the data are apparently incomplete. These are not indicated in detail because many of the delusions demonstrated were of a surface type and were regarded as evasive and inconsequential and, in many instances, as jocular responses. It should be noted, however, that the delusion "the open mouth means death," experienced by fourteen patients, was in every case associated with fantasies and conflicts over oral erotic ideas. Not all the data obtained are included



The chart represents an abstract of the psychologic data obtained in this study. Each entry designates a finding noted in more than one patient. Single findings were omitted for brevity and because they were less significant. In general only the four general symptoms were observed without administration of sodium amytal, and the findings indicated in the lower portion of the chart appeared when maximal amounts of the drug were used. Thus, one might consider the lower entries as representative of more buried mental phenomena.

in this chart, but each notation represents a group of two or more concurrences. It should also be noted that fear of poisoning by enemies (occurring in five patients) was associated in four instances with paranoid ideas based on homosexual fantasies. Mutism "to avoid saying the wrong thing" was frequent, occurring in twenty, or 41 per cent, of the mute patients. Some of its supporting structure is indicated in the chart.

Refusal of Food.—In over half (eleven, or 55 per cent) of the patients refusing food the desire for death was found near the top of the understructure. As the basis of this wish, there was found in two cases a guilt-laden wish—in one, for matricide combined with Oedipus difficulties and in the other, for patricide with persecutory paranoid ideas and overt homosexual acts. The present economic situation is reflected in this group by four patients (20 per cent) whose desire for death was connected with a sense of unworthiness, dependent on inability to live as others do because they were unable normally to earn a living.

Waxy Flexibility.—This symptom was present at some time in twenty (32 per cent) of the patients investigated. The supporting structure in seven patients (35 per cent) was partly at least a feeling of perplexity, which in my analysis remains unexplained and isolated. Here, again, one finds the wish to avoid exposure to reality by not moving, and, thus, not doing the incorrect thing. This occurred in six, or 30 per cent, of the patients in this group. A supporting structure concerning itself with some form of overt sexuality was found in seven patients. This event occurred with greater frequency in connection with members of this group than with any others considered.

Uncleanliness.—It may be noticed that entries in the chart under this heading are fewer than those for any other symptom. As each entry represents at least two concurrences, it follows that the structure on which this symptom rested was the most complex and diverse. No patients manifested this symptom in whom some of the foundation was not elicited.

Inability to Choose Among Different Lines of Action.—This understructure was found in the majority of all patients studied (fifty, or 81 per cent). Its occurrence in the group was as follows:

	Total No. in Group	No. in which Symptoms Occurred	Occurrence of Symptoms, %
Mutism	41	36	88
Refusal of food	20	13	65
Waxy flexibility	20	17	85
Uncleanliness	20	16	53

This symptom is apparently fundamental, and no understructure for it was found. It was the only symptom which occurred universally

as part of the support of all the major symptom complexes studied. Therefore, this unit is more characteristic of the catatonic reaction than any other encountered.

COMMENT

Four common, definite and related symptom groups found in catatonic patients were investigated by a psychopharmacologic method. In these patients, who are otherwise approached with difficulty, a supporting structure was sought for the symptoms presented. Inability to choose among different lines of action was the only constant, fundamental factor found and is considered the most constant psychologic basis on which the catatonic reaction rests. The other phenomena noted did not occur with sufficient frequency to be considered as other than conditioning factors which, with the psychosomatic peculiarities of a given patient, determine the variations noted clinically within the diagnostic limits of the catatonic group.

CONCLUSIONS

1. The psychopharmacologic approach is applicable to determination of the psychologic structure of catatonic reactive states.

2. The basis on which this psychologic structure rests is inability to choose among different lines of action.

3. The variations noted within the diagnostic limits of the group are determined by two groups of factors: (*a*) the psychosomatic peculiarities of the individual patient, and (*b*) his experiences.

REFERENCES TO SEX ORGANS AND FUNCTIONS IN SPEECH PRODUCTIONS OF TWO PRESCHOOL CHILDREN

ABRAHAM A. LOW, M.D.
CHICAGO

That sex interest is strongly developed in infants and preschool children is assumed by some psychiatrists and is a fundamental dogma with psychoanalytic workers. The only warrant for the assumption thus far has been the catamnestic material elicited from normal or psychoneurotic persons. In other words, the dogma of sex interest in children rests on the evidence offered by the utterances of adult persons. After forty years of psychoanalytic effort the literature shows not one attempt, based on numerically representative material, to reverse the process and consult the utterances of children instead of those of adults. Anna Freud,[1] Melanie Klein [2] and Hug-Hellmuth [3] studied the verbal utterances of preschool children; their work, however, was not planned to collect objective data, and their procedure was that of subjective interpretation. Bernfeld,[4] alone of all psychoanalytic workers, seems to have felt the need for systematic collection of material by keeping a diary on his oldest child. However, for no ascertainable reason, he carried the record to the one hundred and fiftieth day only and did not publish an analysis of its contents. The only existing month by month speech record of a child is that kept by the Scupin parents [5] on their son Ernst Wolfgang, but the Scupins contented themselves with publishing their observations without analysis. I know of no attempt on the part of a psychoanalyst, psychologist or psychiatrist to make a comprehensive quantitative, or even a qualitative, study of the material available in the little booklet. Charlotte Buehler [6] had some portions of the Scupin

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Read at the meeting of the Chicago Neurological Society, May 20, 1937.

From the Psychiatric Institute of the Research and Educational Hospitals of the University of Illinois College of Medicine, H. Douglas Singer, M.D., Director.

1. Freud, A.: Einführung in die Technik der Kinderanalyse, Leipzig, Internationaler Psychoanalytischer Verlag, 1925.

2. Klein, M.: The Psycho-Analysis of Children, translated by A. Strachey, New York, W. W. Norton & Company, Inc., 1932.

3. von Hug-Hellmuth, H.: Aus dem Seeleneleben des Kindes, Leipzig, Franz Deuticke, 1921.

4. Bernfeld, S.: The Psychology of the Infant, translated by R. Hurwitz, New York, Brentano's, 1929.

5. Scupin, E., and Scupin, G.: Bubi's erste Kindheit, Leipzig, T. Grieben, 1907.

6. Buehler, C.: Kindheit und Jugend, Leipzig, S. Hirzel, 1931.

diary analyzed by her collaborators and communicated the results, but not the details, of the analysis. In view of the unsatisfactory state of affairs with regard to the problem of sex interest in children, it seemed advisable to collect objective data on the subject and to submit them to a quantitative analysis. The present investigation was undertaken with a view to providing a modest portion of the needed information.

SOURCE OF MATERIAL USED IN PRESENT STUDY

In the summer 1930 two mothers were asked to record daily the utterances of their children, Fred, aged 2 years and eight months, and Nancy Jane, aged 3 years and 2 months, respectively. The mothers were American born, college bred and financially independent. Both children were first born, without physical handicap and to all appearances of good average mentality. At present they are 9 years old and are developing satisfactorily.

The mothers were instructed to record the children's utterances without reference to meaning and interest and to furnish strictly verbatim statements. The record was collected for two years and was discontinued when one of the children, Fred, became increasingly aware of being "written up." After this discovery his utterances were no longer rated as spontaneous manifestations of speech and thought and were considered of questionable value for a study of spontaneous development.

During the two years' period the mothers' productions were discussed in weekly conferences, and mistakes in recording were corrected and eliminated. The mistakes referred mainly to occasional nonverbatim statements.

Aside from a general study of speech and thought, a special study of children's interests was contemplated. It was considered of particular importance at the time to investigate interest in colors and numbers and in the organs and functions of the anogenito-urinary sphere. In these items selection seemed desirable, and the instructions given the mothers specified that utterances referring to these subjects should be recorded whenever possible. The total record must, therefore, be considered to be weighted with reference to the anogenito-urinary sphere.

Altogether, 14,721 sentences were secured by Nancy Jane's mother and 6,997 sentences by Fred's mother—a total of 21,718 sentences collected in the course of twenty-four months.[7]

Nice (A Child's Attainment of the Sentence, J. Gen Psychol. **42**:216, 1933) counted 10,500 words spoken by her daughter during one day of uninterrupted recording at the age of 63 months. G. C. and J. Brandenberg (Language Development During the Fourth Year, Pedagog. Semin. **26**:27, 1919) made a count on a child of 11,623 words for one day at the age of 40 months and of 14,930 words at the age of 52 months. It may then be permissible to conjecture that 10,000 words

7. The proportion of the total utterances of the children contained in the 21,718 sentences is difficult to estimate correctly. The mothers' collections were mere samples, usually recorded at meal-time. In addition, no observations were made on an average of about seven days each month by Fred's mother and of about eight days each month by Nancy Jane's mother, in consequence of traveling, sickness of the child or mother or other preoccupations. The literature contains reports of only a few instances in which the total of a child's utterances was recorded, and even then for a single day only.

per day represents a fair average for the daily speech production for the ages (from 3 to 5 years) tabulated in the present study. On the basis of this estimate, Fred's record contains nearly 1 per cent (89.6 words per day of recording) of his total speech production for a period of two years, and Nancy Jane's record, about 2 per cent (199.3 words per day of recording). Such large samples must be considered numerically representative.

TERMS AND DEFINITIONS

A quantitative study is essentially one of counting, and the items to be counted must be so delimited and defined that the count is rendered independent of subjective bias. It might seem that the title of this paper limits itself to terms that are unquestionably objective, hence reliably countable. On the face of it, there ought to be no difficulty in locating in a given speech record all the statements and questions concerning sex organs and sex functions and to establish their exact numerical incidence. However, the task is by no means simple and requires a set of neat and unequivocal definitions if the count is to be objective and unbiased. The failure to provide such a set of definitions permitted the students of vocabularies to include in or exclude from their compilations whatever item they pleased, and it is the neglect of suitable provisions for rigidly objective countability that is responsible for the sterility of vocabulary studies and similar endeavors. For one thing, the lack of counting standards makes it impossible to compare the results of one author with those of another.

Since the present study was based on a record of sentences, the term "sentence" called for definition. The definition given by the New Standard Dictionary of a "related group of words containing a subject and a predicate with their modifiers, expressing a complete thought" proved unsatisfactory. This formulation would have eliminated from the count all phrases which express a complete thought but lack either a subject or a predicate, e. g., "you naughty girl," "oh, my poor flowers" and "no more soup." Phrases of this kind were considered "equivalents of sentences" and were included in the count. If the phrase consisted merely of "yes" or "no" it was not counted.

There was some difficulty in formulating a working definition of what constitutes a question or statement concerning organs and functions of the various parts of the body. Had it been only a matter of counting the instances in which the children mentioned such terms as "penis," "weewee," "pooh," "hand," "eyes" and "stomach" the task would have been easy. There was, however, the difficulty in distinguishing between the mention of and the mere reference to the item. When Nancy Jane said, "I have a big hand, not a sore hand like yours," she mentioned "hand" twice and referred to it once in the pronoun "yours." The item was then counted three times, because "yours" undoubtedly stood for "your hand." But when she said, "I scratched my face; I wouldn't do it any more," "it" obviously referred to "scratching" and not to "face." In order to avoid ambiguity, the rule was adopted that only the pronominal references should be counted that referred to the body part and to no other portion of the sentence.

At the age of 4 years and 7 months Nancy Jane asked, "Mommie, will your fingers grow any more?" The mother replied, "No." Nancy continued, "Will daddy's?" It is obvious that the word "finger" can legitimately be supplemented in the second question, "Will daddy's (fingers)?" The word was therefore counted twice. However, when the child, at the age of 3 years and 8 months asked, "Have you a pain in the leg?" and, on being given the reply, continued, "So have I," the question arose whether the statement "so have I" called

8. Footnote deleted.

for the supplementation "a pain in the leg" and whether the word "leg" should be counted twice. Such a decision cannot be left to the judgment of the observer but must be regulated by a rule. The rule was adopted that supplementing was permitted only if in the incomplete sentence—"will daddy's?" and "So have I" —no other noun but that referring to the body part was omitted. In the sentence "Will daddy's?" the only noun omitted was "fingers"; in the sentence "So have I" two nouns were omitted ("pain" and "leg"). In the first sentence "finger" was counted; in the second sentence "leg" was not counted. Such difficulties arose infrequently, and the overwhelming majority of body parts were plainly mentioned, such as "leg" or "hand," or were referred to pronominally in a manner that was not subject to ambiguity of interpretation. Since ambiguities were encountered, however, it seemed advisable to test the margin of error. Dr. Irene Case Sherman, of the Psychiatric Institute, volunteered to make a count of a sample of 2,000 sentences, applying the aforementioned rules for counting. Her final count differed from mine in 4 items only in a total of 125 body parts mentioned or referred to in the 2,000 sentences. In other words, the margin of error was 3.2 per cent.

TABLE 1.—*Total Incidence of References to Body Parts in Proportion to Total Number of Sentences*

		References to the General Body Sphere								References to the Anovesical Sphere		References to the Genital Sphere	
	Total Number of Sentences	Upper Extremities		Lower Extremities		Head		Neck and Trunk		Bowels; Buttocks; Urine; "Weewee"; "Pooh"; Toilet; Wetting; "Grunts"		Penis; "Weewee"; Vagina; Testes; "Seeds"	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nancy Jane	14,721	195	1.3	81	0.5	303	2.1	137	0.9	118	0.8	30	0.2
Fred	6,997	110	1.6	35	0.5	126	1.8	69	0.9	79	1.1	7	0.1

ANALYSIS OF MATERIAL

In table 1 the total incidence of references to body parts is analyzed in proportion to the total number of sentences. Under the heading "genital sphere" are listed all the occasions on which the children made mention of "vagina," testis" and "penis" or its equivalent "weewee." At first glance, it appears that Nancy Jane, with 30 references, accumulated a higher record in the genital sphere than Fred, with only 7 references (respective percentages, 0.2 and 0.1). However, Nancy Jane's favorable record is due to a "special training factor." In the period preceding the keeping of the record her mother had leaned toward that trend in modern education which advocates early instruction in matters of sex. The child received a considerable amount of explanations concerning the penis, vagina and testes. In addition, the mother instructed her frequently on child-bearing, explaining it as a process in which "seeds" are planted by the father which subsequently develop into babies. This educational zeal was promptly checked when the study began; it is interesting to note that during the first week of recording, "penis" was mentioned five times and "vagina" and "testis" once each, while in the subsequent twenty-three months the terms "testis" and "vagina" disappeared

completely from the record and the term "penis" recurred only after twenty-one months, when at the age of 4 years and 10 months, it was mentioned three times. Obviously, the interest in these items had been artificially fostered, and it disappeared when the artificial stimulation ceased. The mention of "seed" continued to figure in the record with rather regular frequency, even after the sex instruction was checked. Altogether, Nancy Jane mentioned "seed" twenty times, "penis" eight times and "testis" and "vagina" once each. Whether the term "seed," referring as it does to the process of "bringing of children" rather than to a sexual organ and function proper, should have been tabulated under the heading "genital sphere" is debatable. With the same justification, all items could have been included in which the child spoke of babies being brought from the hospital, hens laying eggs, etc. However, the inclusion of "seed" among the items of the genital sphere was decided on precisely in order to weight that column. If the 20 references to "seed" are eliminated from the count Nancy Jane's record would be reduced to 10 items in the genital sphere, and her percentage would drop to 0.1, equaling that of Fred's.

Fred's mother did not exert herself in the matter of sex instruction, and the 7 references to the genital sphere found in Fred's record were all to "weewee." The terms "testis," "vagina" and "penis" were never mentioned, which is another indication that no sex instruction was given.

Table 1 shows that in both children's records items referring to the genital sphere fall measurably behind their total number of references to the other body spheres tabulated under the various headings. This is all the more surprising if it is recalled that the mothers were instructed to favor items belonging to the sexual sphere and to exempt them from the general rule not to practice selection.

If the references to "seed" are eliminated from Nancy Jane's record, there remain two occasions only, i. e., two days of recording, on which she made remarks about genital items. However, the remarks were couched in the form of questions and may be taken as evidence of interest, even if fleeting. Fred's remarks, on the other hand, were never questions, and the context into which they were fitted demonstrated clearly the absence of curiosity. Quotations will illustrate the point.

On July 28, 1930, at the age of 2 years and 9 months, Fred was at the beach, together with Nancy Jane. Nancy touched Fred's penis, asking, "What's this?" Fred, turning his back, replied, "I take that away." The mother added the comment, "I detected no embarrassment on Fred's part. The reaction might have been the same if Nancy had admired or touched one of his toys." About seven months later, Fred and his cousin Harry undressed together in the bathroom. Harry, who was one year older than Fred, pointed to his own penis and said, "Mine is bigger than yours." Fred, pointing to his abdomen, replied, "What? This?" Harry, again touching his penis, insisted, "No, this." Fred replied, "Well, this (abdomen) is bigger." This manifest lack of curiosity was observed anew in Fred at the age of 4. The two cousins were again in the bathroom, and Harry remarked, "Let's change our weewee, like we did in Michigan City." This presumably referred to a joint act of urination, when the boys spent their summer at a resort. Fred replied, "All right." Harry then commented, "Your weewee is little; you're like a baby." Fred's answer was: "I am as big as you are." It was only after 4 years and 4 months that Fred gave first evidence of spontaneous interest in the organs of the genital sphere. Without provocation, he addressed his mother: "You have a weewee, mommie, inside of you." Mother: "How do you know?" Fred: "I saw a girl have one." Mother: "Which girl?" Fred: "I don't know, for crying out loud." Four days later he remarked to his grand-

mother: "Granny, boys have their weewees sticking out, and girls have theirs inside." The grandmother asked: "How do you know?" Fred: "I saw it." These were the only 2 instances of spontaneous interest in the genital organs found in the total record of 6,997 sentences.

As is evident from table 1, the children scored higher in the anovesical sphere. The items tabulated under this heading referred to "wetting the bed (or pants)" and "going to the toilet." In addition, they contained the terms "pooh" and "urine" or its equivalent "weewee." Nancy Jane's equivalent for "pooh" was "grunts." "Buttocks" was never mentioned by the children, but Nancy Jane, at the age of 3 years and 9 months, while looking at herself in the mirror during undressing, pointed to the buttocks, asking: "Oh, look, what's this name?" Mother: "Buttocks." Nancy: "How do they open?" Mother: "They don't open." Nancy: "How do grunts come out, then?" The term "buttocks" was thus not actually mentioned, but the part was referred to ("they"; "this"). "Bowels" was mentioned or referred to twice by Fred, when, at the age of 3 years and 5 months, he could not be induced to take the soup and gave as the excuse: "I can't eat it, 'cause my bowels move away and they don't come back." To what the term "bowels" actually referred in this instance is not clear, but the 2 items were included among the references to the anovesical sphere, since this sphere was also to be weighted whenever possible.

The references to the general body sphere were subdivided into separate groups and listed under the headings "upper extremities," "lower extremities," "head" and "neck and trunk." Under the heading "upper extremities" were tabulated references to "arm," "finger," "thumb," "hand" and "nail," the last because it never referred to toe-nails. "Elbow," "wrist," "palm," "fist" and "forearm" were never recorded; apparently, the parts were not pointed to, nor questions asked about them. The heading "lower extremities" contains the references to "leg," "foot," "toe," "knee" and "lap." The terms "hip," "heel," "calf" and "thigh" were not mentioned in either record. Under the heading "head" is included every mention of the items "ear," "eye," "eyelash," "eyebrow," "eyelid," "cheek," "face," "forehead," "head," "jaw," "lip," "mouth," "mustache," "nose," "nostril," "tongue," "tooth" and "whiskers." "Hair" was also included because whenever the children mentioned the term, it referred to the scalp. The heading "neck and trunk" contains all the references to "neck," "throat," tonsils," "collar bone," "shoulder," "back," "breast," " heart," "liver," "navel" and "nipple." In addition, all the items which, having no particular localization within the body, could not be grouped under any of the subdivisions, were included under "neck and trunk." They comprise the terms "blood," "body," "bones," "skin" and "skeleton."

ENVIRONMENTAL INFLUENCE VERSUS SPONTANEOUS INTEREST

It would be difficult to point to any single factor that might account for the percentage distribution of the various items in table 1. Yet the fact that the percentages for both children are so closely parallel, and in the instances of "lower extremities" and "neck and trunk" even identical, suggests that some set of principles operates in causing the type of distribution. Two main possibilities offer themselves for consideration: (1) The distribution is due to environmental influences, and those items gain the greatest frequency that are most frequently mentioned by the parents and (2) the frequency with which an item is mentioned depends on a nonenvironmental factor which constitutes a spontaneous interest or trend. The possibility of an environmental factor, among other things, is suggested by the fact that of the 81 references to the "lower extremities" found in

Nancy Jane's record 42 fall to the word "foot," 27 to "leg," 7 to "knee," 3 to "toe" and 2 to "lap." It is reasonable to assume that "foot" and "leg" figure far more frequently in the utterances of the parents than "knee," "toe" and "lap." Presumably, the parents have little opportunity to use these terms in their addresses and their admonitions to the children, while it is probably a common occurrence that they have to urge them to take the "feet" or "legs" off the chair. In this respect, it is significant that certain body parts, such as "elbow," "wrist," "palm," "hip" and "heel," are not found in the record. The reason seems to be that these terms are accidentally or deliberately not mentioned in conversation with the children or that they happen to be mentioned infrequently in any type of conversation. However, the possibility should be considered that they are mentioned with reasonable frequency but, in consequence of a lack of spontaneous interest in them, are not adopted by the children.

That environmental influences play a considerable part in regulating the frequency of use is obvious in such items as "finger," "thumb," "being on the toilet" and "wetting the bed." Both children were thumb-suckers and bed-wetters, and the habits were recurrently condemned by the parents, relatives and maids. The frequency with which the terms were mentioned by the elders accounts, to a great extent at least, for their frequency in the records. If the environmental factor were largely or chiefly responsible for the frequency of use, the low score in the genital sphere would find its ready explanation. Fred's parents never mentioned the terms "penis," "testis" and "vagina" in the presence of the boy, and Nancy Jane's parents ceased mentioning them after they were instructed to do so.

Both children's records contain verbatim quotations of numerous remarks made by the parents, and for some items a fair estimate is possible of the relationship between the frequency of use by the parents and that by the children. "Thumb" figures prominently in the remarks of both Nancy Jane's and Fred's parents. Yet Nancy Jane, whose total number of sentences was double that of Fred's, used "thumb" 6 times to Fred's 45 times. Other differences are equally striking; Nancy Jane used "body" 4 times and Fred 10 times. "Blood" is found 21 times in Nancy Jane's record and once in Fred's, and "throat," 23 times in Nancy Jane's record and once in Fred's. Such wide divergences cannot be explained on the basis of environmental influences alone. The approximately equal use of "thumb" by the parents of both children has been mentioned. With regard to "throat" the situation is similar, both records containing recurring statements about "sore throat," and that Fred's parents mentioned "blood" and "bleeding" with reasonable frequency on the occasion of falls and bruises can be taken for granted. In the case of "thumb" the difference cannot be explained by a possible alternative use of "finger" for "thumb," for the children used the word "finger" with approximately equal frequency—Nancy Jane, 72 times in 14,721 sentences, and Fred, 32 times in 6,997 sentences. Clearly, a nonenvironmental factor of spontaneous interest supplementing the environmental factor must be invoked to account for the mode of distribution.

ATTENTION OF CHILDREN TO THEIR OWN BODIES VERSUS ATTENTION TO OTHER PERSONS' BODIES

In chart 1 the shaded portions represent the items which refer to the children's own bodies, while the blank spaces plot their references to other persons' bodies. In both records the genital sphere shows the lowest incidence of references to the children's own bodies. This seems to suggest that if the children were at all

interested in the organs and functions of the sexual sphere, that interest was only to a small extent focused on the organs and functions of their own bodies. The objection that the total number of references to sex accumulated in the records is too small to permit charting and plotting might hold for Fred, with a total of 7 references, but hardly for Nancy, whose total is 30 references.

QUESTIONS AN INDEX TO CURIOSITY

Table 2 gives an analysis of the interrogatory references in proportion to the total number of questions. Fred's score in the genital sphere is zero; i. e., his mother did not record, and probably never heard him ask, a question concerning genital organs and functions during the entire period of observation. Nancy Jane accumulated a total of 14 questions and apparently established a

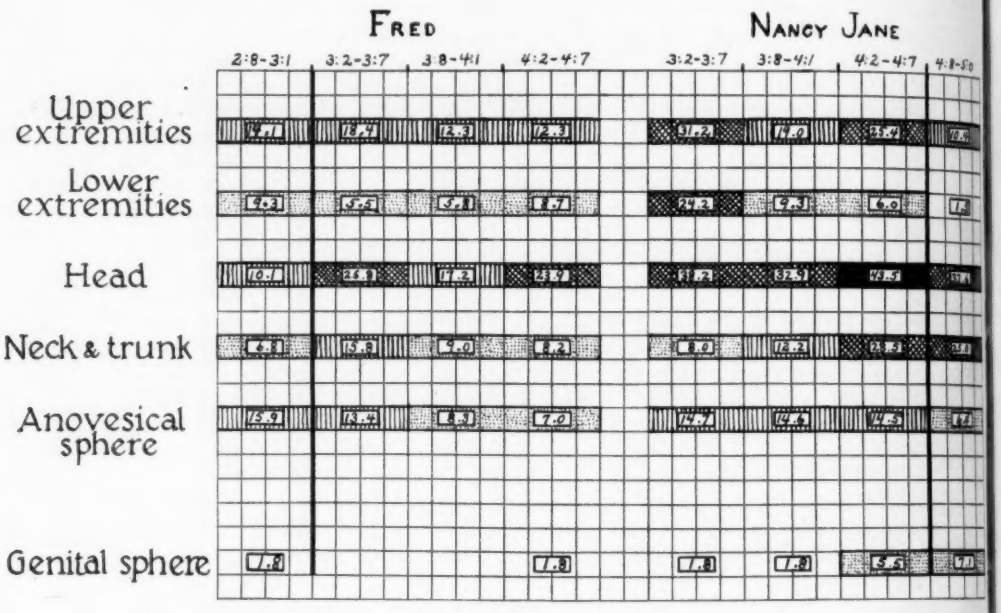

Chart 1.—Ratio of utterances referring to the children's own bodies to those referring to other persons' bodies.

fair record. However, 5 of the questions—about the penis, testis and vagina—were asked during the first week of recording, i. e., at a time when she was receiving frequent sex instruction. During the subsequent twenty-three months she asked only on one occasion a question about "penis." The remaining 8 questions referred to "seed." In other words, her questions were mainly the direct result of the "special training factor" without which her record would be almost zero.

In a previous publication[9] it was pointed out that the sum total of questions found in a numerically representative speech record is a fair index to the

9. Low, A. A.: Studies in Infant Speech and Thought: I. The Development of Sentence Structure in Infancy from the Viewpoint of Grammar, Illinois Medical and Dental Monographs, Urbana, Ill., University of Illinois Press, 1936, vol. 1, no. 2.

curiosity of a child. If this is correct, both children exhibited a measurable degree of curiosity with regard to the various organs and functions of the anovesical and general body spheres, but display of curiosity about the genital organs and functions is absent from Fred's record and figures in Nancy Jane's only to the extent to which it was artificially stimulated.

That the factor of curiosity as measured by the number of questions is expressive of an inner trend may be exemplified by a quotation from the record. At the age of 3 Fred began to use the word "body" and subsequently referred to it, mainly in questions. He pointed to himself and asked: "What's this?" The mother replied: "Your body," whereupon Fred continued: "Why is it a body?" About three weeks later the mother reported: "Fred still is fascinated by the word 'body' and asks about it at least four or five times a week. He points to himself and asks, 'Is this a body, mommie?' I tell him 'yes,' and then he asks, 'Why is it a body?'" One week later the mother's report read: "He is still interested in the word 'body' and mentions it frequently. Fred said to me: 'Where is your body? This is a bath-robe. This is not a body.'" For

TABLE 2.—*Ratio of Interrogatory References to Total Number of Questions*

	Total Number of Questions	Interrogatory References to the General Body Sphere								Interrogatory References to the Anovesical Sphere		Interrogatory References to the Genital Sphere	
		Upper Extremities		Lower Extremities		Head		Neck and Trunk		Bowels; Buttocks; Urine; "Weewee"; "Pooh"; Toilet; Wetting; "Grunts"		Penis; "Weewee"; Vagina; Testes; "Seeds"	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nancy Jane	3,107	39	1.3	14	0.5	71	2.3	29	0.9	9	0.3	14	0.5
Fred	1,309	10	0.8	7	0.5	21	1.6	17	1.3	17	1.3	..	...

the following few weeks the record contains no mention of or questions about "body," until Fred was 3 years and 2 months old. His mother then complained of pain, whereon he remarked, "Mommie, does your body hurt you?" In the subsequent seventeen months the word "body" was mentioned twice, but not in questions. Obviously, at the age of 3 curiosity about "body" took its origin; it then developed cumulatively for a number of weeks and finally declined. The onset, the cumulative increase and the gradual decline of the curiosity cannot be linked to a corresponding sudden appearance, increase and decline of the environmental perception of the experience "body." The feature was manifestly expressive of a spontaneous trend in all stages of its evolution. Similar evolutional phases of curiosity were recorded for other body parts. They were particularly frequent and conspicuous concerning items other than body parts, e. g., "death" and "birth," but were significantly absent for items belonging to the genital and the anovesical sphere.

The aforementioned quotation of Fred's questions about "body" throws a revealing light on the method of recording suggested to and employed by the mothers. Fred's mother expressly stated that "body" was mentioned "at least four or five times a week" for a month. Altogether, the boy must have mentioned the item dozens of times. However, it was recorded 6 times only during that

month. This omission demonstrates how heavily weighted were the genital and anovesical spheres. There, the mothers were always on the alert not to miss any item.

INDEXES

Table 3 gives an account of the number of days on which references to the various items were made as compared to the total number of days on which the mothers took notes. The number of days on which an item was mentioned is thus added as a third index to the factor in the child's reference to the item. The first index is the total incidence of references to the item and is tabulated in table 1. The second index is the number of questions asked about the item, as listed in table 2. Table 3 shows that, as measured by the index of the number of days, both children established the lowest score in the genital sphere.

Analysis of the three tables from the point of view of their respective "index values" is now in place. In table 1 it was shown that Fred mentioned 110

TABLE 3.—*Number of Days on Which References Were Made in Proportion to Total Number of Days of Note Taking*

	Total Number of Days of Note Taking	Number of Days with References to the General Body Sphere								Number of Days with References to the Anovesical Sphere		Number of Days with References to the Genital Sphere	
		Upper Extremities		Lower Extremities		Head		Neck and Trunk		Bowels; Buttocks; Urine; "Weewee"; "Pooh"; Toilet; Wetting; "Grunts"		Penis; "Weewee"; Vagina; Testes; "Seeds"	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nancy Jane	517	97	18.8	53	10.3	156	30.1	74	14.3	61	11.8	13	2.5
Fred	547	62	11.3	30	5.5	81	14.8	37	6.8	42	7.7	4	0.7

times the items belonging to the "upper extremities." Another way of expressing the same fact is the statement that in a record of 6,997 sentences his attention was aroused 110 times (1.6 per cent) by the sight of, or by some other manner of experiencing, the objects "hand," "finger," "thumb," etc. These items, then, had for Fred an "attention-arousing value" of 1.6 per cent. Of the 110 references 10 were questions; table 2 demonstrates that the 10 questions were 0.8 per cent of the total number of 1,309 questions. Since questions connote curiosity (urge to know or to be shown and told), it may be said that Fred's curiosity with regard to the items of the "upper extremities" was aroused to the extent of 0.8 per cent of the total number of questions. Or, to put it differently, the items of the column for "upper extremities" had a "curiosity-arousing value" of 0.8 per cent for Fred. If, now, table 3 is consulted, it is found that the two values for attention and curiosity were displayed on 62 days of the two years of observation, or 11.3 per cent of the total of 547 observation days. The 62 days, or their percentage equivalent of 11.3, represent the frequency or persistency with which the attention and curiosity were aroused. On the basis of this consideration, it seems permissible to say that the items of the column for "upper extremities" had a "persistency value" of 11.3 per cent for Fred. Altogether, then, these items had for Fred an "attention-arousing value" of 1.6 per cent, a "curiosity-arousing value" of 0.8 per cent and a "persistency value" of 11.3 per cent. If these

indexes are added together, a final additive index of 1.6 plus 0.8 plus 11.3 is secured, or a total additive index of 13.7. The additive index is thus obtained by the expedient of combining the "attention index," the "curiosity index" and the "persistency index." However, since the element of curiosity is far more expressive of interest than mere attention and persistency, it was thought that in the elaboration of the final additive index the "curiosity index" should be weighted as compared with the "attention index" and the "persistency index." The final additive index was therefore calculated on the basis of adding 1 times the "attention index," 2 times the "curiosity index" and 1 times the "persistency index." For Fred's items of the "upper extremities" the final additive index is then 1.6 plus (2 times 0.8) plus 11.3, or 14.5.

DEVELOPMENT OF INTERESTS IN SUCCESSIVE HALF YEAR PERIODS

Chart 2 plots both graphically and numerically the final additive indexes for both children in four successive half year periods. Fred's half year periods had

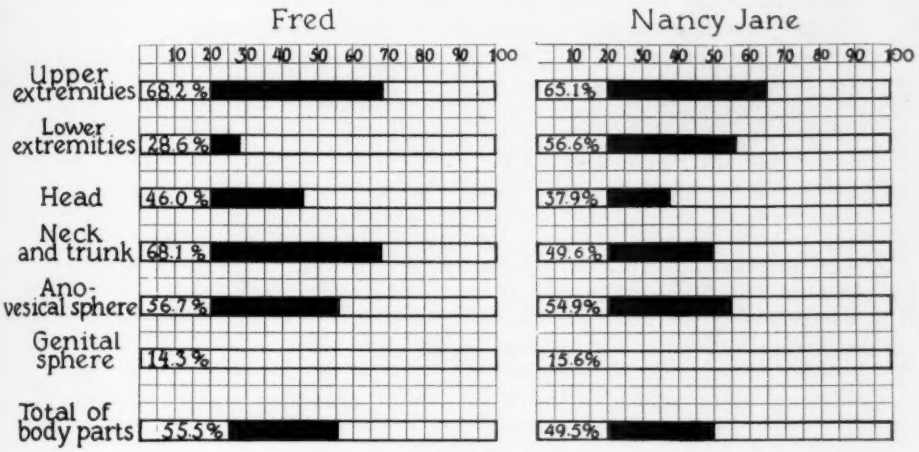

Chart 2.—Additive indexes.

the following range: from the age of 2 years and 8 months to that of 3 years and 1 month; from the age of 3 years and 2 months to that of 3 years and 7 months; from the age of 3 years and 8 months to that of 4 years and 1 month, and from the age of 4 years and 2 months to that of 4 years and 7 months—twenty-four months altogether. Nancy Jane's chart is arranged on the same principle, but her last half year period from the age of 4 years and 8 months to that of 5 years consists of five months only. This is due to the fact that the study of her behavior began one month after Fred's and comprised twenty-three months only. The number in the center of each field represents the final additive index for the half year period, e. g., 18.4 for the half year period from the age of 3 years and 2 months to that of 3 years and 7 months in the column for "upper extremities" of Fred's record and 31.2 for the corresponding half year period in the same column of Nancy Jane's record. The graphic plotting is done by means of differential shading of the various fields. Indexes below 5 are not plotted but are merely inserted as numbers in the center of the field. Indexes below 5 occurred once in Nancy Jane's column for "lower extremities" and twice

in each child's column for "genital sphere." The dotted fields represent the indexes between 5 and 9.9. The indexes between 10 and 19.9 are represented by the fields with vertical lines; those between 20 and 39.9, by the fields with crossed lines, and those above 40, by the black spaces. The chart contains only one such black space for the half year period from the age of 4 years and 2 months to that of 4 years and 7 months in the "head" column for Nancy Jane. The two heavy vertical lines which cut through both parts of the chart separate the first from the second half year period in Fred's record and the third from the fourth half year period in Nancy Jane's record. The three half year periods of each record which remain inside the vertical lines are chronologically comparable.

Analysis of the comparable periods between the age of 3 years and 2 months and that of 4 years and 7 months shows that Nancy Jane leads Fred in the higher brackets of the indexes by a wide margin. Her record has one field with a black space (index 43.5), while Fred's has none. The six fields with crossed lines (indexes between 20 and 39.9) in her record are comparable to the two in Fred's record. If the size of the index numbers is expressive of the intensity of interest, Nancy Jane's record must be considered to be significantly superior to Fred's. This coincides with the general experience gained from studies on differences based on sex [10] that girls tend to develop faster than boys of the same age levels.

The chart illustrates another important difference in the type and rate of development of the two children. If Fred's indexes in the column for "upper extremities" are compared with Nancy Jane's in the corresponding column, it is noted that Fred's progression during the four half year periods is relatively continuous and Nancy Jane's largely discontinuous. Fred's indexes range from 12.3 to 18.4, with a spread of 6.1. Nancy Jane's indexes range from 10.4 to 31.2, with a spread of 20.8. A similar difference is observed in the columns for "lower extremities." Fred's progression is here again conspicuously steady and continuous and Nancy Jane's discontinuous, though steady in the sense of a steady decline in the size of the indexes. In the columns for "head" and "neck and trunk" the progressions of both children are relatively discontinuous, but Nancy Jane's is more so than Fred's, especially in the column for "neck and trunk." The only column in which Nancy Jane's progression is more continuous than Fred's is that for the "anovesical sphere."

What this relative lack of spurts and peaks means in Fred's development must be left to future studies. Obviously, however, in some children, more than in others, development tends toward spurts and peaks. The difference cannot be explained on the basis of a marked divergence of environmental influences. The environmental factors, e. g., the number of items mentioned by the elders, may reasonably be assumed not to have fluctuated so widely as to condition the strikingly continuous decline of indexes from 24.2 to 9.3, then to 6 and finally to 1.5 in Nancy Jane's column for "lower extremities." Nor could they account for the similarly striking ascent of the indexes in her column for "neck and trunk." Clearly, the main factor determining development in the items studied here is in the nature of an inner trend. This trend must be considered stronger in Nancy Jane than in Fred.

The chart shows no difference in trend in the columns for the genital sphere and a hardly noticeable difference in those for the anovesical sphere. That the apparent difference in the columns for the genital sphere—Nancy Jane's rise from an index of 1.8 to that of 7.1—is entirely due to the "special training factor"

10. Wellman, B. L.: Sex Differences, in Murchison, C.: Handbook of Child Psychology, Worcester, Mass., Clark University Press, 1933, p. 626.

has been mentioned. It is remarkable that in spite of the influence of this factor, the index figures for two half year periods for the two children are identical—1.8. Although the statement is subject to verification by future studies, one is tempted to conclude that the only column in which the environmental factor is exclusively or preponderantly responsible for the result is that for the genital sphere. Indeed, if it is recalled that two days only are recorded in which each child made spontaneous references to the genital sphere and that all the remaining references were due either to the "special training factor," in the case of Nancy Jane, or to questions asked by other children, in that of Fred, the inference as to predominance of the environmental factor in the genital sphere seems well founded.

SUMMARY AND CONCLUSIONS

The present paper purports to offer nothing more than the results of the study of two cases. Any conclusions drawn from the tables and charts must refer only to the two children from whose records they are taken. This pointed statement is made advisedly, in order to stress the necessity for further studies of a similar nature. The only generalizing inference which seems permissible is that the two children, being without any noticeable physical or mental handicap, are likely to be representative of an average group. Even so, it is imperative to gather material in many more "cases" before arriving at generalizing conclusions. To mention only one possibility that might lead to faulty generalization: Both children may be too close to the extreme limits of the average group which they otherwise represent.

That "sex interest" in infants can be studied only by means of the case study method ought to be a truism, since the experimental approach is hardly available. What has been attempted here was nothing more than to lift an important and highly controversial subject from the stimulating, but unpromising, region of speculative polemics to the cold and matter-of-fact, but fruitful, province of critical analysis. As it stands, the investigation is incomplete. The items for the genital sphere were perhaps adequately compared with the corresponding items for the other body spheres. A detailed comparison, however, with other topics of interest—"death," "birth," "time," "marriage" and "age"—is missing. In a future publication [11] a comprehensive study of these interests will be furnished and the deficit supplied.

An attempt to sum up the results of the analysis will confine itself judiciously to the points that follow directly from a study of the tables and charts. It seems definitely established that both environmental factors and spontaneous trends were operative in directing the children's attention and curiosity to the items of the various body parts. The main environmental factor was the frequency with which the parts were mentioned by adults in the environment. That in the case of Nancy Jane another environmental factor was introduced in the form of delib-

11. Low, A. A.: Studies in Infant Speech and Thought, Illinois Medical and Dental Monographs, Urbana, Ill., University of Illinois Press, to be published.

erate training has been mentioned repeatedly. The factor of spontaneous trend presented itself in the form of curiosity as measured by the number of questions. Analysis showed that while both children asked a sizable number of questions about all the nongenital spheres, they had in the genital sphere either a low record of questions (Nancy Jane) or a zero record (Fred). The factor of spontaneous curiosity must therefore be considered as practically nonoperative in the children's attitude toward the genital sphere. The fact that no more than 16.7 per cent of Fred's and 15.6 per cent of Nancy Jane's references to the genital sphere dealt with the organs of their own bodies points in the same direction of lack of spontaneous interest in their own sexual organs and functions. The frequency with which the parts were mentioned by the adult members of the family (environmental factor) could not be appraised with any degree of accuracy, since no adequate record of the parents' remarks was available. However, for Nancy Jane it is certain that most of her references to the genital sphere were directly traceable to the "special training factor," and that Fred's references, up to the age of 4 years and 4 months, were all made in response to comments of other children has been properly stressed. All in all, the conclusion seems inevitable that both children's references to the genital sphere (1) were numerically insignificant, as compared with the number of references to the other body spheres, and (2) were mainly prompted by environmental factors, to the almost complete exclusion of the factor of spontaneous interest.

DISCUSSION

Dr. Alfred P. Solomon: In attempting to evaluate Dr. Low's results with personal clinical experience, I recall many instances in which children between the ages of 3 and 4 years are stated to have been subjected to sexual experiences or information on sex by older children, associated with a pledge and warning never to tell their parents. The manner in which these pledges are observed until the children, as adolescents or adults, are given an opportunity for the first time to tell the experience to a psychiatrist indicates that the episode was not commonplace and that large motivating forces must have preexisted to have enabled these children to maintain such a prolonged silence. I refer not to repressed material but to consciously suppressed verbalization of the experiences in the presence of repeated conscious emotional thinking about them. Such patients have said that "hardly a day has passed when I haven't thought of the experiences."

While Dr. Low's statistical results in these 2 cases are interesting, I wonder whether statements made by these children to their parents are a true indication of what they were thinking. The thought content, after all, is the source of any substantial etiologic deduction.

Dr. D. M. Olkon: Dr. Low's investigation, as I understand it, did not concern itself with repression or other activities of the children. All he claims to have done was to instruct the mothers to keep a daily diary of the children's talk and to record specifically any spontaneous mention by the children of any organ of the body, and of the sex organs in particular. These objective data in tabulation show clearly that in these children awareness of the sex organs in particular as compared with that of other organs of the body was least apparent.

It seems to confirm the common observation that children of the age studied are least concerned with their sex organs.

DR. FRANCIS J. GERTY: Any attempt to apply scientific methods in a psychiatric problem always meets with the criticism that such methods cannot be applied. For that reason, I wish to compliment Dr. Low for making this attempt, even though he could study only a limited corner of the problem.

DR. THOMAS M. FRENCH: Statistics are good evidence, when it is possible to interpret them, but one does not know just what Dr. Low's statistics mean. In fact, Dr. Low said in his conclusions that he did not know what they mean. To understand statistics of this sort, one would have to study them in the light of the total psychic situation of the child. How freely a child will talk to its mother about sex and about its excretory functions will depend to a large extent on the attitude of the parents toward such matters and on whether the child expects that the parents will approve of its mentioning the genitals or excretory products. Children of from 3 to 5 years have all undergone some training in control of the sphincters, and this is apt to leave behind it inhibitions with reference to these physical parts, as well as with reference to the genitals. Statistics such as those reported by Dr. Low can therefore be understood only if one knows in detail the character of the child's training and the exact way in which the child has reacted to that training.

I also notice that Dr. Low classifies birth and marriage as topics not related to sex. In so doing, I think he inevitably will exclude as nonsexual the two topics that are the subject of the child's most lively sexual curiosity—the question of where babies come from and that of what the parents do with each other, of what marriage consists.

Finally, I think that most of Dr. Low's references to psychoanalysis are attempts to knock down a man of straw. Psychoanalysis has found evidences of a lively interest in the genital functions dating from the age of from 3 to 5 years and of a keen interest in the excretory products dating from an even earlier age, but no psychoanalyst has ever maintained that children are interested only in sex. Along with the sexual urges are the drives concerned with self-preservation and the ego, and the main functional task during this period obviously is growth and learning to master the environment. This, of course, has always been known. Freud's contribution consisted in demonstrating that along with the drives concerned with the ego children also have sexual urges of considerable intensity, which, however, in most instances normally undergo quick repression. In this connection it is of interest to mention a frequent experience of parents who attempt to make explanations of sex to children. In many cases the child will already have developed inhibitions with reference to the topic of sex that will cause it to reject the proffered explanations as something that should not be discussed. Dr. Low's statistics must therefore be regarded as a resultant of the conflict between a child's spontaneous interest in sex and its fear and inhibitions.

DR. MEYER SOLOMON: Dr. Low has reported on 2 children studied between the ages of 2 and from 4 to 5 years. Claims about infantile sexuality have been made for years by Freud and his school. By the way, I think the original statements by Freud were claims rather than findings. Melanie Klein (Psychoanalysis of Children, authorized translation by Alix Strachey, New York, W. W. Norton & Company, Inc., 1932) stated that even in infants of from 6 months to 2, 2½ or 3 years there are sexual tendencies wilder than the average adult ever dreamed of. It seems to me that all work of a truly critical nature on speech and behavior of children from earliest infancy is of great value. The majority of students of children, so far as I know, do not agree with the views of Freud. This paper represents a practical study and presents nothing to support the claims of Freud. If it is asserted that studies of this sort on infants between the ages of 2 and 5 years do not disprove, at least in some measure, the claims for infantile sexuality because repression already exists, it permits one to make any claims

one wishes for the infantile period before speech and then to discount any findings for the developmental period of active speech of from 2 to 5 years of age. Furthermore, it seems to me that interest in birth and marriage is not to be included under the term "sex" if one gives sex the meaning that the rank and file of humanity do. If one allows for repression, the attitudes of the parents and the like, even the figures given by Dr. Low do not show that the infants had any sexual feeling or desire in the sense that one ordinarily uses the term "sex." They merely show interest in words (which may be mere word play) or in sexual organs, without any connection with so-called sexual desire. I should say that the remarks of Dr. French apply to a later period than that of from 2 to 4 years, during which, according to my limited observation, children do not know or think much about marriage, sex and birth. They may ask a few questions, but, so far as I know, if they are given a reply that satisfies them, there is no evidence that there is any great, persistent interest in the subject.

Dr. Thomas M. French: I should like to mention an incident in the life of a child whom I have followed closely. This child was brought up with a very careful attempt on the part of both parents neither to encourage interest in sex or infantile sexuality nor to be unduly severe in the repression of sexual manifestations. Nevertheless, the child acquired control of its bowels rather prematurely, and the mother on a few occasions showed undue impatience. Some time after control of the bowels had been acquired, I think at the age of about 2½ years, the child woke in the middle of the night with a nightmare. On being questioned as to what was the matter, he gave definite evidence of fear that he had defecated on the floor. Nothing especial was said about that, but in the subsequent period he showed an acute phobia of a spot anywhere around a room. Shortly after this period the child went on a vacation during which the family lived in an old house. There was a spot on the ceiling where the masonry had been repaired, and the child experienced an acute phobia about sleeping in that room because of the spot. This occurred immediately after he had had the fear that he had made a spot on the floor. Nothing was done except that the mother was instructed to be especially careful not to reprove the child for making spots in the bed. Once or twice he expressed the fear of soiling the bed, and the mother took especial pains to let him feel that this was not very bad. Under the influence of this treatment, the child became less anxious about soiling. Shortly afterward, when the father was lying down, the child spread a blanket over him and played he was putting his father to bed. He ended this play by instructing his father not to soil the bed. That was the end of the phobic manifestations.

In this instance it is easy to see that in spite of the parents being careful not to be too energetic in training the infant in sphincter control, the child acquired nevertheless a definite fear of soiling; it was rather difficult to release him from that fear. In the light of such experiences it is obvious that statistics like those of Dr. Low mean nothing unless they are correlated with the whole picture of the child's emotional life. The number of remarks the child makes about sex is an indicator not of the child's interest in sex but rather of the outcome of a conflict between sexual interest and inhibitory forces. It is impossible to understand the statistics without knowing something about the child.

Dr. A. A. Low: In this debate all are in a fair degree of agreement. It is agreed that nothing was proved or disproved by my paper, as I stated in my concluding remarks. What is not agreed on are a few items mentioned by Dr. French. I do not doubt that affect is important in the child's reactions to matters of sex, but no matter how important, affect cannot be studied objectively. The fact is that in order to elicit objective data some items must be selected that can be assayed quantitatively, regardless of whether the item selected is more or less important. Its relevance can be determined only by subsequent investigation. The present approach is quantitative, but limited in scope. One ought to have, as Dr. French suggests, a complete record of the statements made by the parents. But it must not be forgotten that all that was intended was to present the reports

of 2 cases. Other cases will have to be studied. One of my associates is keeping an extensive record of the utterances of her child, and I hope the "case" will soon be reported.

A valid objection was raised with reference to the difficulty of determining whether a given item refers to the genital or to some other sphere. In other words, criteria for selection must be determined and the probable error established. Both the criteria of selection and the probable error are covered adequately in the paper. The probable error is 3.2 per cent.

Dr. French stated that the items of birth and marriage could be included among the references to the sexual sphere. If so, the door is left open for arbitrary selection. By the same token, "hat" could be included among the items for "head," and "shoes" and "socks," among those for "lower extremities."

GERSTMANN SYNDROME: FINGER AGNOSIA, AGRAPHIA, CONFUSION OF RIGHT AND LEFT AND ACALCULIA

COMPARISON OF THIS SYNDROME WITH DISTURBANCE OF BODY SCHEME RESULTING FROM LESIONS OF THE RIGHT SIDE OF THE BRAIN

J. M. NIELSEN, M.D.
LOS ANGELES

"Body scheme" or "body pattern" is the concept which a person has of the structure of his own body or that of another and the relations of the parts of the body to each other. This body scheme may be disturbed without the patient's becoming aware of it spontaneously and the disturbance may even fail to cause any defect so far as performance of purely motor functions is concerned. The body scheme may be affected in whole or in part by focal lesions in the parietal or the parieto-occipital region. Such lesions do not necessarily affect projection tracts but involve association systems and cause genuine disturbance of the psyche.

There are certain peculiar differences, however, in the types of disturbance of the body scheme resulting from lesions of the two sides. Destruction of the major area, usually the left, by lesions of certain types or locations produces defects on both sides of the body; destruction of the minor area produces defects on the opposite side only. There are other differences, particularly referable to orientation as to laterality and the sense of direction, which result only from lesions of the major side. There is thus an analogy with apraxia, in which in certain cases a lesion of the left side produces apraxia on both sides, while a lesion of the right side or of the corpus callosum affects one side only.

SYMPTOMATOLOGY OF LESIONS ON THE MAJOR (LEFT) SIDE

In 1924 Gerstmann [1] described a new syndrome, of finger agnosia, agraphia, confusion of right and left and acalculia. The finger agnosia was considered a disturbance of orientation and consisted in failure of the patient to recognize, show and name the fingers of either hand,

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1. Gerstmann, J.: Fingeragnosie: Eine umschriebene Störung am eigenen Körper, Wien. klin. Wchnschr. **37**:1010-1012, 1924.

in spite of sufficient vision and tactile sense. There was no difficulty in recognition of other objects by vision or touch and no other sensory or motor disturbance of the fingers. With hemianopic narrowing of the visual fields to help in the localization, Gerstmann concluded that a lesion was probably present in the inferior part of the left parietal lobe. Autopsy was not performed in this case.

In 1926 Herrmann and Pötzl [2] reported another case of the syndrome which differed from the preceding in some respects. The main point of difference was that the patient was ambidextrous and the lesion was on the right side. In addition, however, and apparently because of this laterality, the patient showed certain signs of involvement of the minor parietal lobe, namely, forgetting of the left limbs; they had disappeared from his spontaneity. The authors made the diagnosis of a lesion at the border between the right angular gyrus and the second occipital convolution; this was verified first at operation and later at postmortem examination. As the lesion was neoplastic, other symptoms made their appearance with its expansion.

By 1927 Gerstmann [3] had seen two other cases, one of a large neoplasm, with verification at operation, and the other of softening in the area described by Herrmann and Pötzl. In 1928 Isakower and Schilder [4] reported a clinical case in which the condition was due to poisoning with illuminating gas. One could not, of course, expect a purely focal syndrome under these circumstances, and aberrant symptoms were present. Kroll and von Rad [5] each reported a case in which there was an added symptom, loss of opticomotor nystagmus. In the case of von Rad there were also aphasic and other difficulties—amnesic aphasia, alexia and ideational apraxia.

Lange [6] produced two papers on the subject—the first in 1930, in which he reduced the disturbance in this syndrome to the one basic fault disturbance of direction in space, and the second, much more detailed, in 1933, in which he enlarged on his original concept. These accounts are among the most valuable in the literature to date. A monographic account of agnostic disturbance, including disturbances of body

2. Herrmann, G., and Pötzl, O.: Ueber die Agraphie und ihre lokaldiagnostischen Beziehungen, Berlin, S. Karger, 1926.

3. Gerstmann, J.: Fingeragnosie und isolierte Agraphie—ein neues Syndrome, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:152-177, 1927.

4. Isakower, O., and Schilder, P.: Optisch-räumliche Agnosie und Agraphie, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:102-142, 1928.

5. von Rad, C.: Kasuistischer Beitrag zur Symptomatologie der Herderkrankungen in der Uebergangsregion des Parietal- und des Occipitallappens, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:273-288, 1930.

6. Lange, J.: (*a*) Fingeragnosie und Agraphie (ein psychopathologische Studie), Monatschr. f. Psychiat. u. Neurol. **76**:129-188, 1930; (*b*) Probleme der Fingeragnosie, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:594-610, 1933.

scheme, has also appeared from Lange's pen in the *Handbuch der Neurologie*.[7]

Between Lange's first and second paper Marburg [8] (1931) reported a somewhat similar case in which autopsy was performed. It differed from those previously reported in that agraphia was absent. Marburg ascribed the finger agnosia in his case to a lesion in the supramarginal gyrus. There was, however, also a lesion in the angular gyrus, but, on the basis of the ages of the two, he arrived at the differentiation. In the same year, in a valuable article in which he surveyed the situation, Schilder [9] pointed out that up to that time there had been described in these cases five conditions which were to be considered in relation to disturbance of finger function. He showed that these subdivisions were not merely academic but that each had a distinct localizing value. They may be listed as follows:

Condition	Location of Lesion
1. Optic finger agnosia	Lesion in this condition nearest the occipital pole
2. Finger agnosia	Transition zone between the angular gyrus and the second occipital convolution
3. Constructive finger apraxia	Between the region for finger agnosia and the supramarginal gyrus
4. Apraxic disturbance in finger selection	Supramarginal gyrus
5. Finger aphasia	Extension of Wernicke's zone

To this situation was added in 1932 the case of Zutt in which there were disturbance of right and left, constructive apraxia and agraphia, but no finger agnosia. This made it evident that the syndrome of Gerstmann is not an inviolable entity. It appeared as though each element might, if completely understood, have separate localizing value.

At this point the second article of Lange [6b] appeared. In it the author described a case of a visual agnostic variant of finger agnosia. He pointed out that in the case of Conrad there was finger aphasia but no agraphia, that in the case of Schlesinger [10] there was finger apraxia and that in other cases finger agnosia was dissociated from almost all the other symptoms of Gerstmann's syndrome, although it had never

7. Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 10.

8. Marburg, O.: Scheitellappenerweichung unter dem Bilde eines Pseudotumor cerebri (Zugleich ein Beitrag zur Frage der Fingeragnosie ohne Agraphie), Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:1-13, 1931.

9. Schilder, P.: Fingeragnosie, Fingerapraxie, Fingeraphasie, Nervenarzt **4**:625, 1931.

10. Schlesinger, B.: Zur Auffassung der optischen und konstruktiven Apraxie, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:649-697, 1928.

been seen alone. Essentially, he agreed with Schilder as to the localizing value of the elements.

In the same year Engerth [11] reported observations to show that associated with finger agnosia there is at times disturbance of drawing of high degree, especially for the face and hands. The defect last mentioned he considered an indication of autotopagnosia for these parts. Feuchtwanger [12] stressed constructive apraxia in his cases and pointed out the essential difference between this and the classic forms of apraxia. In 1934 Mussio-Fournier and Rawak [13] reported a case of the Gerstmann syndrome in which autopsy was performed. In this case the urine of the patient had a melanophorotropic reaction in the frog. In 1932 Schilder [14] presented the first paper in the English language, a survey of the subject, and in 1935 Muncie [15] reported two cases studied in Europe under Lange.

In all the verified cases of this sort which have been reported to date there was a lesion in the major parieto-occipital area. For the Gerstmann syndrome itself the lesion is generally accepted as being at the border of the angular gyrus and the second occipital convolution on the major side. An excellent case is presented here, with report of the autopsy.

CASE 1.—*Finger agnosia, agraphia, confusion of right and left, constructive apraxia, loss of ability to draw, disorientation in time, no aphasia; typical capsular hemiparesis. Autopsy showed metastatic carcinoma of the adrenal, with three lesions in the brain: the first in the left thalamus, the second (subcortical) at the border of the left angular gyrus and the second occipital convolution and the third, a small lesion, lying parasagittally in the left forceps major.*

History.—H. L. D., a white man aged 49, was admitted to the general medical service of the Los Angeles County Hospital on July 6, 1936, because of pain and weakness in the lower extremities. He stated that he had been troubled with wheezing in the chest for two years but had not been ill until five weeks before, when he had been compelled to cease his ordinary work as a carpenter because of onset of intense pain in the lumbar region. The pain had been in the nature of a constant ache which spread down the limbs; after two weeks at home weakness had developed so that he was barely able to walk.

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11. Engerth, G.: Zeichenstörungen bei Patienten mit Autotopagnosie, Ztschr. f. d. ges. Neurol. u. Psychiat. **143**:381-402, 1933.

12. Feuchtwanger, E.: Ueber optisch-konstruktive Agnosie (zugleich ein Beitrag zur Pathologie der optischen Vorstellungstätigkeit), Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:469-496, 1934.

13. Mussio-Fournier, J. C., and Rawak, F.: Glioblastome de l'hémisphère gauche avec syndrome de Gerstmann. Réaction mélanophorotrope sur la grenouille par l'urine de la malade, Rev. neurol. **2**:681-685, 1934.

14. Schilder, P.: Localization of the Body Image (Postural Model of the Body), A. Research Nerv. & Ment. Dis., Proc. **13**:466-484, 1932.

15. Muncie, W.: Finger Agnosia (Gerstmann), Bull. Johns Hopkins Hosp. **57**:330-342, 1935.

Approximately at the time of onset of the weakness, he awoke one morning unable to speak as before. Difficulty with speech was of two types: inability to articulate clearly and trouble in finding the words he wanted. The latter symptom never became severe, but the thickness of speech progressed, so that at the time of examination it was with considerable effort that one could understand him.

Details of the medical examination are not given here, as they are not germane to the subject at hand. Autopsy revealed primary carcinoma of the right adrenal gland with generalized metastasis. The pain of which the patient had complained was due to involvement of the retroperitoneal nerves and lumbar plexuses.

Neurologic Study.—Consultation was first requested by the intern, Dr. Louise Powers, who thought the patient had aphasia. His inability to write was corroborated by the resident physician, Dr. Elinor Ives, who urged more detailed study. It was my opinion at first that there was no real agraphia, as the disturbance of speech was clearly dysarthria and writing was difficult because of weakness of the right hand. Only when it was found that the patient was totally unable to write with the left hand was a detailed study made.

During the two weeks of examination there were no changes except in degree, for which reason one recording is sufficient. During that time the agraphia gradually increased to completion.

General Motor Function: There was slight weakness of the right lower part of the face, more marked in emotional expression than on voluntary movement. However, the upper limb, especially the hand, was more affected on the right. Although the patient could make a few marks with a pencil held in the right hand, he could not hold it tightly enough to write well. The paresis was specific, and not merely part of the general weakness of the body. He had severe dysarthria, but the difficulty in finding words of which he had complained at the onset was not noticeable.

General Sensory Function: There was general loss of sensation in the lower limbs, more marked peripherally and shading off to a point above the knees. This affected the senses of touch, temperature, vibration and position. Pain on passive motion was extreme. One could not test for a Kernig sign, because the heels could not be raised off the bed without severe pain. Passive movement of the hip joints was much more painful than that of the ankles and toes. There was no other objective sensory loss.

Except for weakness of the right lower part of the face there was no involvement of the cranial nerves. With the expectation of finding defects, we gave special attention to the visual fields, but they were normal.

General Psychic Function: The patient was remarkably alert and in general was clear mentally. This condition continued until two days before death. However, he was fatigued rapidly, for which reason examinations of necessity were short. He was oriented clearly for place and person but not at all for time. This failure stood out in remarkable contrast to his general condition. On July 25 he said that the day was January 8. When the accuracy of this answer was questioned, he stated that at least it was the latter part of January. He did not know the day of the week, nor at 9 a. m. was he sure whether it was morning or afternoon.

His intelligence was above that of the average. He formerly had worked as a draughtsman in the office of an architect and consequently had been able to draw and calculate well. He particularly understood plans and illustrations.

Writing: On July 17 Dr. Ives corroborated Dr. Power's statement that the patient was unable to write. He could not write even his own name or the

word "window" on dictation. He made only unintelligible scrawls. He was able to copy slavishly if the sample was constantly before him. On the other hand, he could construct words on dictation with anagram blocks. He thus built up the words "window" and "boat" on dictation and the word "bag" spontaneously, but all with considerable hesitation and many errors, which, however, he went back to and corrected spontaneously. Three days later he also built up for me the words "New York" on request. At no time was he able to construct even a short sentence, either on dictation or spontaneously. When he found it impossible, he declared, "I am hopeless today." When asked to write "25" he made first a "5" and then placed a "2" before it.

Drawing and Constructive Apraxia: In spite of considerable experience with drawing, he was unable to draw a face or a hand. In the result of his efforts there was not the slightest resemblance to the object represented. His lines were placed one on top of the other, apparently without any sense of direction. The presentation of a sample made little difference. Although he had often drawn a roof with a dormer-window, he could not do so on request. He was also unable to construct a square and a Y with matches, although he succeeded to a fair degree in building a triangle and a T after a sample had been presented. It was necessary, however, for him to look at the sample constantly in order to do this.

Reading: There was never any disturbance in reading. The patient read whatever was presented to him and the newspapers.

Recognition of Objects: He recognized all objects shown him. He named correctly pictures of a baby, Uncle Sam and a cat. He identified playing cards and even interpreted correctly action as shown in still pictures.

Apraxia: There was no apraxia except the defects in drawing and writing. He handled all objects about him without trouble and with dexterity in the left hand. With the right hand he had difficulty because of weakness.

Revisualization of Images: The patient was able to some extent to revisualize former images. He described well known public buildings correctly in some details but made flagrant mistakes in others. He did not know with what kind of roof his house was covered, in spite of his interest in architecture.

Orientation for Right and Left: The patient was entirely disoriented as to right and left. He could not point to parts of his body with either hand, except those in the midline. This applied not only to parts of his own body but to the limbs of the examiner as well. He was unable to tell to which side any given finger belonged.

Finger Agnosia: He had lost identifiability of the fingers. This was a definite defect of recognition, not merely one of naming. It was also distinct from the question of laterality; i. e., mistakes were constantly made with reference to laterality, but the patient could not recognize the fingers even on one hand. At times he gave correct answers. Mistakes were made constantly with regard to the three middle fingers; the occasional correct answers referred to the thumb and little finger.

He was unable to show a given finger on request or to imitate finger postures. Vision did not guide him; at all times during this test he was allowed to look at his hands. There was also no astereognosis. Mistakes in naming fingers were not so constant as errors in presentation of a finger for which the examiner called. There was, therefore, less finger aphasia than finger agnosia. There was no difficulty in identification of toes.

Calculation: Calculation was faulty, but not absent. He gave correct answers to 4×7, $3 + 9$ and $9 + 5$, but 2×3 was 12, and $4 + 7$, 14.

Observations at autopsy are shown in the illustrations.

Of the elements of the Gerstmann syndrome, the patient presented finger agnosia, agraphia, confusion of right and left and partial acalculia. He also showed marked disturbance of drawing, as reported by Engerth,

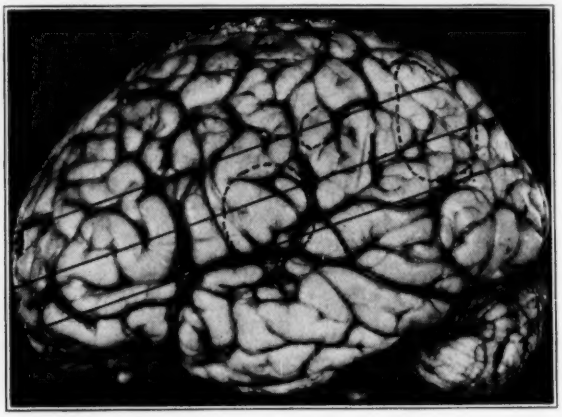

Fig. 1.—Photograph of the left side of the brain in case 1. The parallel lines indicate the planes of section resulting in the views shown in figures 2, 3 and 4. The lesions observed on section have been projected on the surface of the figure and outlined in dotted lines. Nothing appeared on the surface except bulging of the cingulate gyrus to the right, opposite the thalamus. Microscopic examination showed metastatic carcinoma.

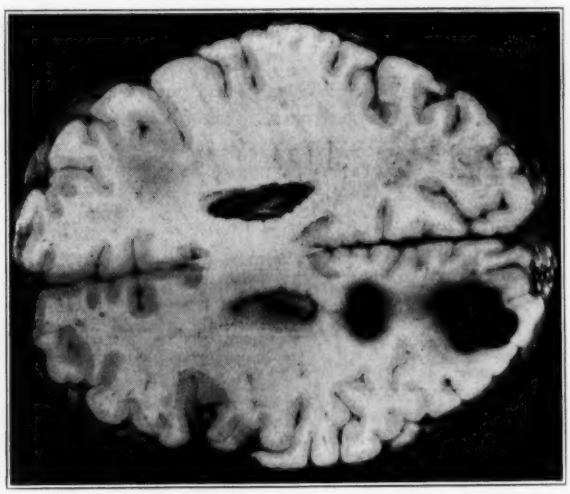

Fig. 2.—This view shows two lesions. The larger is located exactly at the border between the angular gyrus and the second occipital convolution (areas 39 and 19 of Brodmann), but is subcortical. The smaller lesion is farther forward in the forceps major and might be described as subcortical in the gyrus cinguli (areas 23 and 31 of Brodmann).

and the "constructive apraxia" of Kleist; yet the lesion, although subcortical, was exactly in the spot indicated for the Gerstmann syndrome by Herrmann and Pötzl. The disorientation in point of time is cautiously referred to the smaller lesion, which was located subcortically in areas

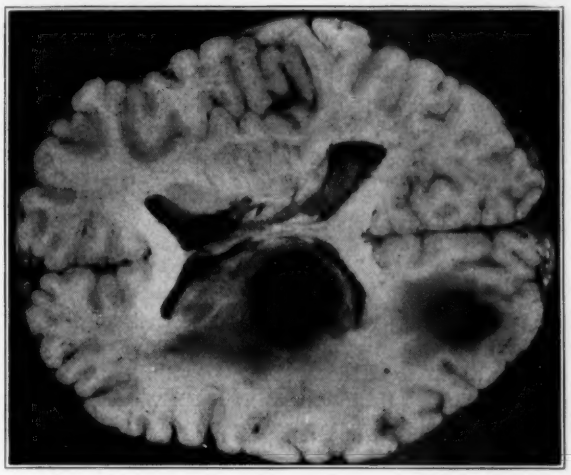

Fig. 3.—This view shows the lower portion of the large lesion illustrated in figure 2 and a third lesion in the thalamus. The ventricular pattern is displaced to the right. This lesion explains the dysarthria and the right hemiparesis.

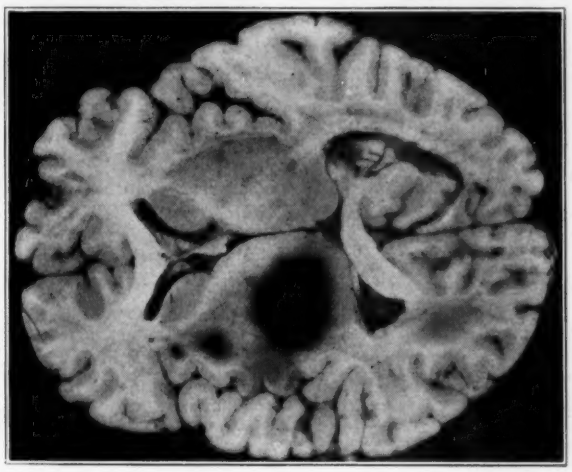

Fig. 4.—This view shows the large lesion in the thalamus illustrated in figures 2 and 3. There is also a suggestion of two other very small lesions, one in the putamen and the other in the insula. These are so small, however, that they are not considered as having had any material influence on the clinical picture.

23 and 31 of Brodmann. The symptoms of capsular and thalamic involvement were entirely explained by the large lesion in the left thalamus.

A second case, but one in which the picture was much more complicated, is next described in abstract, with report of the autopsy. The patient was seen in consultation with Dr. Carl W. Rand,[16] who reported the case as one in which there were false localizing signs due to reactive gliosis.

CASE 2.—*Finger agnosia, agraphia, specific drawing defect, acopia due to constructive apraxia, alexia and disorientation in space; diffuse temporal symptoms, such as uncinate fits, dream states and amnesic aphasia. Operative and postmortem verification of the lesion.*

D. K. W., a physician aged 46, suffered over a period of three months from colored visual hallucinations in the right eye, uncinate fits with dream states and headaches.

Examination for disturbance of body scheme and aphasia revealed finger agnosia, agraphia and acopia, as well as a considerable variety of aphasic manifestations. There was no disturbance of the sense of laterality. All errors in identification of fingers concerned recognition of the fingers themselves, not that of right and left. The patient was unable not only to write but to copy. He looked at the sample but could not plan or execute even a simple figure and could not draw the simplest line. He did better in spontaneous writing, in which he formed a few letters.

Whether he was able to calculate I could not determine absolutely because of severe amnesic aphasia and alexia. He read a "7" and, though unable to read a "9," said that it was two or three points higher than the "7." Such indefiniteness would in all probability cause acalculia. Because of amnesic aphasia he could not calculate in his head.

He had also right homonymous hemianopia and complete disorientation in space although he was oriented in time.

Observations at operation and autopsy are shown in the diagram. Besides the relatively small tumor seen in the left posterotemporal and occipital lobes, there was extensive softening extending forward into the temporal lobe and upward under the angular gyrus. The border between the angular gyrus and the second occipital convolution was therefore affected. This is in harmony with the accepted localization for the Gerstmann syndrome.

A third case follows in which verification was made at operation.

CASE 3.—*Gradual onset over a period of three months with headache, vomiting and agraphia. Examination revealed also finger agnosia, confusion of right and left and mild constructive apraxia. Slight ideokinetic apraxia.*

E. J., a woman aged 42, had been well prior to three months before examination, when there gradually developed increasingly severe headaches, with attacks of nausea and vomiting. One month before she had noticed considerable difficulty in writing, and by the time of examination this had become complete agraphia.

16. Rand, Carl W., and Halsey, W. Howard: False Localizing Signs of Cerebral Tumor, Bull. Los Angeles Neurol. Soc. **2**:84-88, 1937.

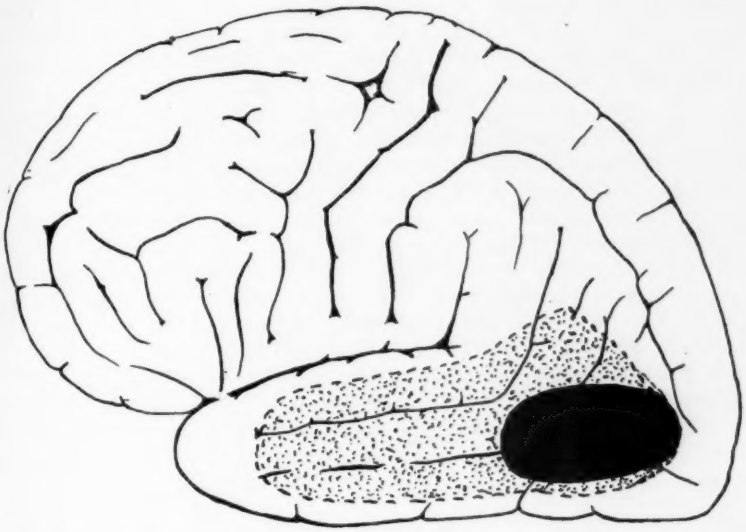

Fig. 5.—Diagram of the lateral view of the brain in case 2. The solid black area indicates the tumor, and the stippled area, the softening.

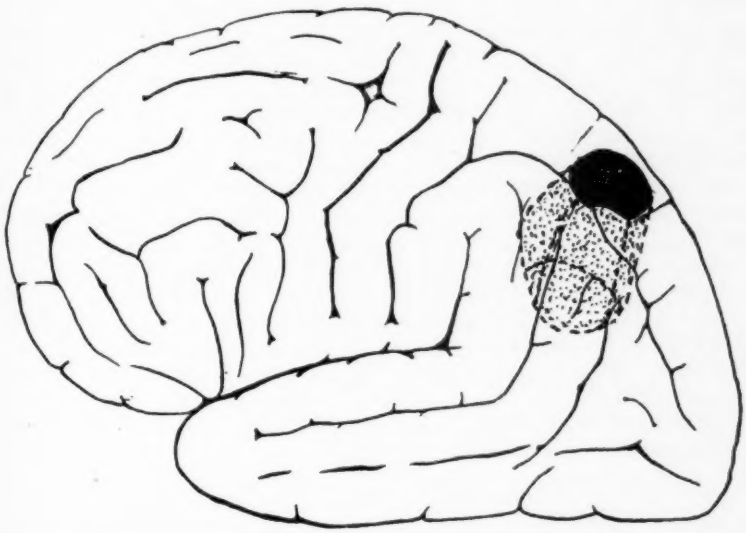

Fig. 6.—Diagram of the lateral view of the brain in case 3. The solid black area indicates the surface extension of the tumor, and the dotted area, the deep portion.

During the examination, on Feb. 12, 1927, the patient vomited frequently and could not be moved because it increased the gastric distress. She lay quietly on her back and cooperated well; because of dehydration and weakness, however, she was fatigued easily. On the preceding day Dr. Carl W. Rand found complete right homonymous hemianopia, which after intravenous injection of sucrose, became incomplete. Bilateral choking of the disks was present, in spite of severe myopia.

Aside from the preceding symptoms, the usual examination revealed no localizing signs; the deep reflexes were neither increased nor diminished, and the superficial reflexes were equal. The Babinski phenomenon was present bilaterally, being slightly more marked on the right. There was no sensory loss.

Agraphia was severe and was of the aphasic, not apraxic, type (letters were well formed, but words were not produced). The patient was unable to write spontaneously; on a request to write "Arizona," she wrote "Awrng." For "England" she wrote "Evganra." She had a little less difficulty with figures, once writing "R" and another time "3" for "5." She wrote "4" for "42."

She was completely confused regarding right and left and the identity of fingers. Only exceptionally did she name a finger correctly, and her demonstration of fingers which were named for her was often wrong. The confusion of laterality applied to the fingers, hands, knees and ears. She finally said she was "all mixed up."

I neglected at the time to test for acalculia.

There was no disturbance in reading, revisualization of distances or directions or orientation in time. She showed a slight constructive apraxia in copying a small bird-house without a roof but drew a square and a circle fairly well. She had great difficulty in cutting with scissors (ideokinetic apraxia). There was no aphasia of any sort, except in naming fingers (part of finger agnosia).

A diagnosis of a tumor was made—probably a spongioblastoma, in the region of the border between the angular gyrus and the second occipital convolution on the left. It was thought that the lesion was superficial, since the hemianopia was incomplete, and that it came to the surface, since the patient could still read.

On the following day, after another intravenous injection of sucrose, the finger agnosia had largely disappeared, but the agraphia remained. After another twenty-four hours the finger agnosia had returned. On this basis, one could not be certain of the exact location of the neoplasm.

Dr. Rand performed an exploratory operation on February 15 and observed a spongioblastoma which came to the surface near the parasagittal border of the precuneus, in the location shown in figure 6. It originated partly below the cortex of the angular gyrus and partly under the second occipital convolution. Its lower pole was at the point where the diagnosis of its center had been made. After removal of the neoplasm, another syndrome appeared, but it does not concern the subject at hand. It will be reported elsewhere.

A fourth case, that of a variant of the Gerstmann syndrome without finger agnosia, is reported clinically.

CASE 4.—*Left handedness; apoplectic onset of left hemiplegia; disturbance of right and left; constructive apraxia; partial agraphia and acalculia; no finger agnosia.*

R. G., a white man aged 56, was well until Nov. 27, 1936, when he awoke raving "like a maniac," and paralyzed in the left extremities. He said he was left handed. Examination at the Los Angeles County Hospital showed that the blood pressure was 144 systolic and 100 diastolic; the peripheral arteries were

considerably sclerosed. There were left hemiparesis and a Babinski sign bilaterally, but no hemianopia.

In examination for disturbance of body scheme, Dr. Ives found confusion of the right and the left side; I verified this as affecting the face and hands. There was never any confusion concerning the feet. This symptomatology persisted for several days and gradually disappeared.

The patient was unable to draw the simplest figure or to cut with scissors so simple a figure as a square. He finally produced a piece of paper with irregular sides. He was also unable to construct any figure with matches, even after a sample had been presented.

He was able to multiply 3 by 4 and 3 by 7, but any figures above this level were beyond him. He made many errors in writing, misspelling words, duplicating letters or condensing. "New York" was unrecognizable.

In spite of all these difficulties, however, he had no finger agnosia. While he made mistakes in identification of right and left in regard to fingers, he never mistook the fingers themselves. This was true even at the height of the trouble.

In the course of twelve days the patient made a great deal of improvement and was discharged; he was still weak in the left limbs and made some mistakes in writing.

I have had opportunity to study a fifth case clinically, but because of signs of bilateral lesions, there were additional elements not related to the Gerstmann syndrome. The case is particularly instructive, however, because of complete loss of sensation in the left limbs without loss of these limbs from the body scheme.

CASE 5.—*Apoplectic onset with hemiparesis; recovery from the paresis; some degree of finger agnosia. Constructive apraxia and finger aphasia; disturbed visualization of body scheme; ideokinetic apraxia of the left limbs; finger apraxia on the left; awareness of the presence, but not of the location, of the left limbs; allachesthesia and dysesthesia on the left side; inability to draw; disorientation in time.*

History.—J. C., a Mexican laborer aged 50, claimed to have been well prior to July 21, 1936, when, while sitting in his garden, he lost balance on leaning forward and fell to the ground. On arising, he found that the left limbs were too "weak" for him to walk about with comfort, and he was taken into the house. There he called a physician, who gave him medicine, the nature of which is unknown to me. As the patient did not improve, he was advised to seek hospitalization.

The history obtained from him on admission included the statement that he had suffered from headache and pain in the lumbar region of the spine for three days and weakness of both lower limbs for two days. He was unable to enlarge further on the history. The headache was generalized, and the pain in the back was located mostly in the region of the fourth and fifth lumbar vertebrae.

Examination.—The patient was well nourished and of sthenic habitus; he was 69 inches (175.26 cm.) tall and weighed 190 pounds (86.2 Kg.); he had the musculature of an athlete but walked with a peculiar gait, projecting his left foot before him as though it were stiff. The foot was slightly everted, and the toes and ball of the foot turned upward as he walked. The left hand assumed peculiar postures, not constant but changing, as observed from day to day. They resembled somewhat athetosis, except that the disturbances were those of posture rather than of movement. He used the left upper limb automatically, but not in planned actions.

General physical examination revealed nothing worthy of note except a blood pressure of 190 systolic and 110 diastolic and arteriosclerosis. There was no definite source of embolus.

Neurologic Examination.—There were a normal sense of smell, essential unimpairment of visual acuity and no constriction of the fields of vision. Examination of the fundi showed normal physiologic cups but sclerotic arteries. There was no nystagmus or diplopia, and extra-ocular movements were normal. The trigeminal nerve was normal, but there was marked disturbance of sensation about the face, as recorded later. The seventh, eighth and ninth cranial nerves were normal, and the tenth nerve was objectively so, though the patient said that since onset of the illness his voice had changed to a deeper pitch than before. The eleventh and twelfth nerves were normal.

The essential difficulty was as follows: Sensory Disturbance: The patient was unaware of the location of the left upper and, to a slight extent, of the left lower extremity. The loss was more marked distally than proximally. He could not tell which finger I grasped, nor even that any had been grasped unless he saw the act. He was not sure even that I had hold of his hand. When I held up his left hand and asked him to take hold of it with the right, he had no idea where to begin to place his right hand. He found it most expedient to start at the shoulder and follow up to the hand. If by chance he found the finger of my hand before he reached his own, as happened several times, he was content that he had found his own and so announced. Any portion of the body which could not be moved about like the hand was found without difficulty with the right hand. The sense of vibration was entirely lost on the left side of the body and the left limb. Sense of touch was lost on the left side—less markedly over the face and most in the extremities, and of the latter, more in the hand than in the foot.

Pain on pin-prick was perceived but not localized correctly. The allachesthesia was marked, the patient saying that he felt on the hand a pin-prick actually present on the foot or the leg. If the stimuli were summated, it was found that he perceived the more accurately the more times he was pricked in rapid succession on the same spot. He thus appeared not to feel the first prick but invariably felt the fifth or sixth. He explained that he felt the sensation not as pin-prick but as electricity. This also applied to sensations of extreme heat and moderate cold. He often misinterpreted heat as cold. Slight differences in heat and cold he failed to distinguish. In passing a continued pin-prick from the left to the right side of the body or vice versa, he said that it became sharper each time the midline was crossed.

To all the preceding observations there were at times exceptions in that the patient gave correct answers unexpectedly. He could not continue this for more than a few trials, however. He thus located and interpreted correctly a few times the pulling of hair on his legs or forearms. Occasionally he also correctly perceived touch.

In general sensation was normal on the right side of the body; there seemed to be a zone of hyperesthesia at the level of the third or fourth dorsal segment, which was not consistent.

Sensation as recorded was determined with the eyes closed. With the eyes open the patient also had difficulty in identifying fingers, especially of the left hand. On the left hand, moreover, he had difficulty in designating by name or number any particular finger. He also had trouble in demonstrating fingers, but this was a motor phenomenon, as will be made clear later. He had no difficulty in differentiating between right and left and no agraphia.

Motor Disturbance: With the eyes closed, the patient was unable to place the hand where he chose, apparently because of lack of knowledge of the position. However, this was not the only difficulty, for when his eyes were open he had similar trouble, consisting in loss of ability to initiate a movement. While lying quietly on his back with the left upper limb beside him, he was unable on request to raise the arm or to put it to his nose, ear, chest, hip or trunk on the same or the other side. In each effort the same difficulty made its appearance, namely, he could not initiate any movement. The same was true when he was sitting up. The left upper limb remained beside him. In spite of much pulling at the shoulder and writhing and twisting the body, and even moving the lower limbs up and down and kicking, he was unable to produce motion in the arm. If he tried long enough (a minute or more) he usually obtained some result and approximated the act requested. He thus brought his hand to his nose or his chin instead of to his ear, or he succeeded only to the extent of bringing the hand on his chest. In a number of attempts to put his left hand on his right knee, he succeeded in raising it into the air. He then brought his knee up to the hand and claimed that he had solved the problem.

In a number of attempts he found it impossible to supinate the hand. When it was lying pronated at his side and he was asked to turn it over, he found it impossible to do so. On another occasion he was lying in bed on his back, with his left hand behind his head. He was asked whether he could put his hand to his ear. He said that he could. He was then asked to tell first where the hand was. He said it was lying on his chest. Even a casual look in its direction would have answered the question for him, but he thought he knew where it was. Whenever he succeeded in getting the hand started in any movement, he did much better than one would have expected on observation of his first attempts.

The foregoing description of the left upper limb applies to it as a whole. There was still more difficulty with the fingers alone. He was unable, even with full vision, to place his fingers in any position requested of him. He could show one finger, but not two. He could not place together the tips of the thumb and the middle finger or those of the little finger and the thumb. Such acts were greatly facilitated by his first doing what was requested with the right hand. In fact, if he was allowed to perform with the two hands simultaneously, he did fairly well. This applied also to acts with the hand as a whole.

The foregoing description of loss of ability to move and perform with the left upper limb and hand applied also, but to a much less extent, to the lower limb. Thus, he could not place the left heel on the right knee, even with his eyes open. The heel passed far above or to the right. He could perform well with the right heel.

When asked what he thought of this disturbance, he explained that he could not command the left hand or foot. He also stated that he could not visualize beforehand what posture the limb should assume or how to make it go there. His apparant difficulty in getting started, he explained, was in picturing to himself what sort of movement he should make to obtain the desired attitude. When this had been figured out, he was able to do fairly well. However, he admitted that even when he had completely figured out what he was to do, he could not command the limb in question. There were thus two types of disturbance—one of ideational plan, the other of the motor act itself.

In automatic acts the patient did fairly well. He could catch with either hand a ball, a piece of crumpled paper or a slipper which was thrown at him, unless the left hand had to pass to the right side of the midline to do so. He also used the left hand to open or to close a door, to raise himself off the bed or to pull the covers over him (characteristic of apraxia).

Certain tonic attitudes assumed by the left hand resembled athetosis, as already stated. This became especially manifest when he tried to write. He wrote with the right hand on dictation. When asked to write with the left hand, he tried to place the pencil in this hand but could not take it. When he compelled the left hand (by means of the right) to take the pencil, he finally succeeded in making the hand hold it. After this he could write. Under guidance of the eyes, he wrote the first half of the word "California," after which the hand trailed off somewhat. However, being a laborer, he was not used to writing. He copied a small bird-house with each hand—as well with the left as with the right. When he had finished performing with the left hand, he tried to take the pencil with the right hand, but the left would not let go. He tugged and pulled, but to no avail. He said: "That's the funny part that bothers me; I can't get the hand to loosen up when I want it to." After some effort, he gave a stronger tug than before; just then the left hand let go "of its own accord," and the pencil came without resistance. The release was so sudden that the right hand jerked the pencil far away. He felt foolish and snickered. The prolonged grasping was not a grasp reflex or the tonic reflex of Walshe, as the hand became fixed thus in various postures.

Drawing: On August 11 there was demonstrated specific inability to draw. This came about during a study of apraxia when the patient was asked to cut a square from the middle of a piece of paper with a pair of scissors. He began to cut, with the intention of cutting a square of about 4 inches (10 cm.). He could not make the angles even approximately correct; so he kept on trying to improve until he had an irregular figure only about 1 inch (2.5 cm.) in diameter. He was dissatisfied with the result but could not improve it. He was next asked to cut out an undrawn triangle. The result was the same. He was asked to cut out a smoking pipe. Even after he had been shown how to do it, he failed. He was next asked to draw, but the result was the same. He could not draw even the simplest geometric figures or the profile of a human face. With matches he could build neither letters nor anything but the simplest geometric figures.

Orientation: He localized sounds correctly, no matter from which side they came. He revisualized images correctly and described the color of grass and the sky without hesitation. He also described the plan to his house.

In spite of excellent general mental function, he was completely disoriented as to time. He did not know the day of the week or the date and could not estimate the length of time he had been in the hospital. He had no elicitable delusions.

Laboratory Data.—The spinal fluid was clear but was contaminated with blood, owing to trauma. The Wassermann reaction was negative. A blood count showed 5,200,000 red cells and 7,150 white cells per cubic millimeter. Of the latter, 58 per cent were polymorphonuclear cells, 38 per cent lymphocytes and 4 per cent morionuclears. Examination of the urine revealed nothing pathologic.

Course.—After three days there was rapid improvement in the condition. The patient became aware of the position of the limbs, and sensation returned. Allachesthesia disappeared, and sensory discrimination was reestablished. At this point the patient still had apraxia of the fingers. He was yet unable to show any number of fingers on command or to perform dextrous movements with them. This condition also affected the forearm to the extent that on effort to place a finger to the ear the hand went to the chin and gradually scraped its way to the ear.

In this case, in spite of complete loss of sensory perception of the limbs, these parts were not lost from the body scheme. I postulate a lesion of the centrum semiovale above the right thalamus, which affected the callosal fibers and was sufficiently high to permit escape of the optic radiation. There must also have been a lesion of the left parieto-occipital area, probably reaching forward to the gyrus supramarginalis, in order to cause the specific loss of ability to draw, finger apraxia, elements of finger agnosia, finger aphasia and constructive apraxia.

SYMTOMATOLOGY OF LESIONS OF THE MINOR (RIGHT) SIDE

The symptomatology referable to the body scheme resulting from lesions of the minor side is utterly different from that due to lesions of the major side. It affects only the opposite side of the body and, instead of manifesting itself only in the terminal portion of an extremity, involves both the opposite limbs, or even the entire left side of the body. The nomenclature of these conditions has been confusing, but in the following discussion an effort will be made to clarify the situation.

At a meeting of the Neurological Society of Paris on June 11, 1914, Babinski [17] reported his observations on patients who were hemiplegic but denied the fact, even after failure in attempts to use the affected limbs. His designation of this condition as anosognosia was unfortunate in that the term signified lack of knowledge of disease in general instead merely of hemiplegia with which the patients suffered. This impropriety of nomenclature becomes prominent when one realizes that von Monakow,[18] twenty-nine years earlier, had described lack of knowledge or recognition of blindness, and that Anton,[19] fifteen years earlier, had described the condition presented by Babinski and had added to this lack of recognition of blindness and deafness. Logically, lack of knowledge or recognition by the patient of any disease he may have is anosognosia.

Moreover, at the meeting just referred to there arose considerable discussion, the effect of which was to diffuse the applicability of the term still more. While Pierre Marie pointed out that visceral as well as somatic disease might be ignored and Gilbert Ballet called attention to lack of recognition of blindness, Henri Meige suggested that it might be the limbs, and not the paralysis, which were unrecognized. He said

17. Babinski, J.: Troubles particuliers de la conscience chez hémiplégiques, Rev. neurol. **22**:845, 1914.

18. von Monakow, C.: Experimentelle und pathologisch-anatomische Untersuchungen über die Beziehungen der sogenannten Sehsphäre, zu den infrakortikalen Opticus centren und zum N. Opticus, Arch. f. Psychiat. **16**:151 and 317, 1885.

19. Anton, G.: Ueber die Selbstwahrnehmung der Herderkrankungen des Gehirnes durch den Kranken bei Rindenblindheit und Rindentaubheit, Arch. f. Psychiat. **32**:1, 1899.

that to the patient it was as though the paralyzed limbs had never existed, and Souques expressed the opinion that the condition was a forgetting of the affected side.

It is clear from this résumé that, without so intending, the discussers caused subsequent cases, entirely different from those of Babinski, to be categorized with cases of anosognosia. In some instances patients have forgotten their limbs or the limbs have disappeared out of their spontaneity without hemiplegia being present. I shall report a case of this sort.

CASE 6.—*Episodic forgetting of the left side of the body without hemiplegia; diminution of all forms of sensation and one jacksonian seizure affecting the left limbs; tendency to deviate to the left; coarse ataxia of the left hand; increase of deep reflexes on the left. Spongioblastoma of the superior part of the right parietal lobe verified at operation. Permission for autopsy refused.*

W. C. W., aged 48, was apparently well up to August 1935 and was occupied daily with his work as a dentist. At this time his wife noticed a slight change of personality in the form of alternating irritability and jocosity. She thought this to be a transient indisposition and gave it little consideration. After about a month she noticed that in driving his automobile he at times deviated to the left. This was particularly noticeable as he approached safety zones, because he repeatedly drove into them and narrowly avoided striking pedestrians who stood there. At such times when he had maneuvered the car out of the awkward situation, he again deviated to the left, so that his wife found it necessary constantly to warn him to keep to the right.

He slowly became less dextrous with his work, so that he had to remake items which formerly had been easy for him. While this irritated him, he nevertheless insisted on doing all his own work, his euphoria and jocosity carrying him through such trying events.

The next important occurrence was a convulsive seizure, which had characteristics of the jacksonian type. This occurred while he was sitting on the toilet. He had first a sensory experience of warmth and numbness in the entire left hand. This was followed by falling to the left and jerking of the limbs on the left side. From the history he was able to give, he apparently lost consciousness for a short time. After this attack the patient was not as well as before. Also, there developed a strange series of events. On several occasions he undressed the right half of his body and went to bed with the left side still dressed. He did not notice this until his wife called his attention to it. In taking a bath, he dried the right side of the body, threw the towel over the left shoulder and left it hanging there. He then began to dress without drying the left side. His wife found him in this difficulty. He repeatedly forgot the existence of the left side of the body. He thought it was funny, laughed it off, as he had done with many other difficulties, and continued his daily work. At times he felt as though his left hand were grasping something, though there was nothing in it.

After this he began to suffer with severe headaches, which were always in the right frontal and temporal regions. The headache was especially a feeling of pressure and was at times so severe that he felt as though the top of his head were going to crack open. In certain attacks consisting of paresthesia of the ulnar side of the left forearm and headache, he became severely nauseated and had projectile vomiting.

During December 1935 the headache became more and more constant until, when I first saw him, it was continuous. He had become less patient and, having decided that there was something seriously wrong, insisted on having "something done." He was unconcerned about the outcome, except that he did not wish to live if incapacitated.

Examination.—The condition had been studied and the patient carefully examined by Dr. P. J. Edson, of Pasadena, Calif., and Dr. D. A. Charnock, of Los Angeles; so my examination was confined to the nervous system. Mentally the patient was perfectly clear, and there was no evidence of aphasia (he was right handed). He gave a good account of his illness but was jocose out of proportion to the occasion. At times this manner was set aside, and in a serious tone he demanded action. He wished to have an operation, regardless of outcome, and asked that in case an inoperable condition were discovered the surgeon should press a pair of forceps into the medulla. This was said not in a tone of despair but as a matter of business. He said he did not wish to be a burden to his wife.

Symptoms of Involvement of the Parietal Lobes: Hypesthesia of the entire left side of the body for touch, temperature, pain, sense of position, sense of vibration and tactile discrimination was noted. The patient was unable to locate the left hand in space with the right without the sense of vision. On the other hand, he could locate the right hand with the left. There was gross ataxia of the left hand resembling a coarse cerebellar tremor. This seemed to depend on loss of sense of position in the left hand. (The tendency to fall straight backward might also be related to the parietal lobe.)

Cranial Nerves: Examination showed anisocoria, the left pupil being 3.5 and the right 2.5 mm. While the right pupil responded well to light, the left reacted poorly. There was marked myopia, the fundi being seen best with a —20 lens. The veins were overfilled and the margins slightly indistinct, but changes characteristic of choked disks were not seen. The fields of vision were normal. Speech was slightly slurring, but the patient's wife stated that it had always been so. The cranial nerves were otherwise normal.

The deep reflexes were greater on the left side, and there was a Babinski sign bilaterally. The patient had talipes equinovarus on the left, a congenital defect. The hemoglobin content was 92 per cent, the red cell count 5,360,000 and the white cell count 5,500, 76 per cent of which were polymorphonuclears. The Wassermann reaction of the blood was negative. A spinal puncture was not made, owing to danger in the presence of a tumor.

Diagnosis.—The diagnosis was tumor of the brain. The question was that of location. The jacksonian seizure indicated either a frontal or a parietal situation. The persistent sensory signs and, above all, forgetting of the left half of the body indicated a parietal location.

Operation.—The patient was referred to Dr. Carl W. Rand. At operation he turned down a large bone flap covering the right frontal and parietal areas. A tumor, about 4 cm. in diameter, was observed in the right superoparietal region and was removed with cautery. It proved to be a spongioblastoma.

Course.—After surgical intervention the patient had left homonymous hemianopia and left hemiplegia. He did not speak of the hemiplegia during the three days of life after the operation (anosognosia ?). He was too ill for detailed study. Permission for autopsy was refused.

An unverified case in which the same symptoms appeared was studied and reported, with the collaboration of Dr. Ives.[19a] In this case there was a complicated disturbance with apraxia, but the episodic amnesia for the left upper limb was striking. A quotation (page 136) follows:

> Another important element was an episodic amnesia for the left upper limb. If it was placed at his side where it was not readily visible and he was asked to place his left hand to his mouth, he complied with his right hand. When we complained that he had not done what we asked, he insisted that he had done it. When we explicitly explained that the hand he had used was the right one and that we had asked him to use the left one and asked him where the left one was, he said, "Why, it is on the left side." He then held it up and demonstrated it. . . . When we stuck him with a pin on the left hand he said it was the right one. The same applied to the foot. It was repeatedly shown that unless he could see the left hand, he forgot that he had it. All requests for performance with it resulted in action with the right hand until we called his attention to the left one.

In these cases there was no lack of awareness of disease and, moreover, no hemiplegia. The cases differ materially from those of Babinski in that in the latter the patients never forgot their limbs; in fact, they remembered them as well limbs and expected to be able to use them. It was the paralysis that they forgot. Further, loss of sensation of the limbs, even of their presence, is not of necessity associated with loss of knowledge of them, as shown in case 5.

In view of these cases, it is clear that consciousness or unconsciousness of the limbs is a separate matter from, and is not associated with, Babinski's anosognosia.[20] Psychic disturbances of body scheme are of all degrees, and these degrees seem to depend on the psychologic constitution of the patient, as well as on the site and extent of the lesion.

The mildest psychic disturbance of this type is episodic amnesia for the limbs. Besides cases 6 and 7, instances of this sort are reported in the literature. The case of Alajouanine and his associates[21] and case 2 of von Stockert[22] belong here. Psychologically, the disturbance is disappearance of the limbs from the attention rather than from consciousness. The simple expedient of calling the limbs to the attention of the patient for the time being abolishes the defect.

The truth of the preceding statement was beautifully shown in a case described by Dr. Clarence W. Olsen at a meeting of the Los Angeles Neurological Society, Jan. 14, 1937.

19a. Nielsen, J. M., and Ives, E.: The Motor Nature of Apraxia, Bull. Los Angeles Neurol. Soc. **1**:133-140, 1936.

20. Babinski, J.: Anosognosie, Rev. neurol. **11-12**:365-367, 1918.

21. Alajouanine, T.; Thurel, R., and Ombredane, A.: Somato-agnosie et apraxie du membre supérieur gauche, Rev. neurol. **1**:695-703, 1934.

22. von Stockert, F. G.: Störungen des Körperschemas und ihre Projektion in der Aussenwelt, Arch. f. Psychiat. **103**:310-313, 1935.

A Negress had suffered a "stroke" two years before which had left her with left homonymous hemianopia. Recently, she had had another cerebral vascular accident, leaving her with left hemiplegia. She denied that the affected limbs were hers and said that "yours," or another's were in bed with her. When she was shown that they were attached to her and that the arm in question merged with her shoulder and that it must be hers, she said: "But my eyes and my feelings don't agree, and I must believe my feelings. I know they look like mine, but I can feel they are not, and I can't believe my eyes."

In some instances the delusion can be argued away. This was shown in the case of a Negress who was admitted to the Los Angeles County Hospital with left hemiplegia.

When asked to hold up her left hand she held up the right. When she touched her left elbow she said it was "some one else's knee." Speaking of her left extremities she said: "That's an old man. He stays in bed all the time." When asked whether she did not mind she replied, "Yes, I don't want any spirits in bed with me. That's my brother-in-law's hand." When she touched her left arm with her right she said: "That's some old meat. That's part of my brother-in-law's arm." However, when she was shown that the arm was continuous with her shoulder she said it must be her own arm. She then also claimed her foot, saying, "My old, rusty foot."

The next more severe disturbance is disappearance of the side from consciousness (case of Barkman [23]). This condition, as Koch and von Stockert pointed out, is negative. It shoud be distinguished from the positive state of feeling of absence of the limbs. The simile that the former corresponds to *hemianopsie nulle* as the latter does to *hemianopsie noire* is apt. In the first case reported by Koch and von Stockert [24] there were attacks of feeling of absence of the side. In case 2 in their report, in case 3 of von Stockert and in the case of von Pap,[25] there was a constant feeling of absence of the affected side. I wish to distinguish between a feeling and a delusion of absence of the affected side. The former is a mere sensation which the patient does not accept at its face value, while in the latter, owing to the dysesthesia, the patient's judgment is affected to the extent of accepting the erroneous report as a fact.

Delusion of absence of the affected side occurred in both the cases of Zingerle,[26] in the second of which the patient even had erotic experi-

23. Barkman, A.: De l'anosognosis dans hémiplégie cérébrale: Contribution clinique a l'étude de ce symptom, Acta med. Scandinav. **52**:213-254, 1925.

24. Koch, J., and von Stockert, F. G.: Störungen des Körperschemas und ihre Projektion in die Aussenwelt mit besonderer Berücksichtigung der akustichen Allästhesie, Klin. Wchnschr. **14**:746-748 (May 25) 1935.

25. von Pap, Z.: Ein Fall von Thalamus-Syndrom mit Störungen des Körperschemas, Monatschr. f. Psychiat. u. Neurol. **89**:336-347, 1934.

26. Zingerle, H.: Ueber Störungen der Wahrnehmung des eigenen Körpers bei organischen Gehirnerkrankungen, Monatschr. f. Psychiat. u. Neurol. **34**:13-36, 1913.

ences through contact with the "absent" left side, which he thought belonged to a woman. During one episode in this case, there was amnesia for the side.

Comment.—In cases of anosognosia gathered and summarized by Barkman there were hemianopia and hemiplegia. In the three cases of the series in which autopsy was performed a lesion of the right thalamus was observed. Barkman expressed the opinion that the trouble in genuine anosognosia is failure of the sensory impulses to reach consciousness. With this I agree.

On the other hand, in cases of amnesia for the side, with extension of this loss psychologically dependent on various factors, there need be neither hemianopia nor hemiplegia, and the thalamus need not be affected. This is a genuine disturbance of body scheme resulting from a lesion anatomically nearer the cortex than that in the preceding group and psychologically on a higher level of integration, and it is a true disorder of the psyche.

In two cases reported by Ives and Nielsen [27] in which postmortem studies were made, the lesions were chiefly above the thalamus (in one instance affecting it slightly, however). In the first of these cases the patient denied possession of the limbs, saying they were "yours" or "the doctor's." When directly questioned he said, "they are not mine." The lesion was small, affecting the retrolenticular part of the internal capsule and, to a slight extent, the thalamus. In the second case the patient said: "Some one is substituting this arm (pointing to the left) for my left arm," and "my wife rubbed this arm, but it wasn't my arm." The lesion was large, the entire right parietal lobe being softened.

COMPARISON

Comparison of disturbances of body scheme resulting from lesions of the two sides shows, then, that lesions on the major side, in the area necessary, cause disturbance of knowledge of the two hands, especially the fingers. It seems, as many authors have pointed out, that the major parieto-occipital region is a correlation area in which the hand is specifically converted from an organ to a tool in the service of the body as a whole. There is in the same region a laterality-coordinating area, a lesion of which causes loss of the sense of right and left, and even entire loss of sense of direction. The more closely the lesion approaches the occipital pole, the more of a visual element one finds in the disturbance. The nearer the lesion approaches the parietal region, the more of a sensory element there appears. The more closely the lesion

27. Ives, Elinor R., and Nielsen, J. M.: Disturbance of Body Scheme: Delusion of Absence of Part of Body in Two Cases with Autopsy Verification of Lesion, Bull. Los Angeles Neurol. Soc. **2**:120-125, 1937.

approaches Wernicke's zone, the more of a language, or symbolic, element one finds.

On the other hand, a lesion of the minor parietal region causes, when disturbance of body scheme appears, a dropping out of the opposite side of the body, first from the attention and then from consciousness. Depending on the psychic make-up of the patient and the extent or exact site of the lesion, there may be severe mental defects, even to the extent of delusion of absence of the side.

In pondering over the reason for the differences as outlined, I believe that the question of handedness is the crux of the matter. This, in turn, seems to depend on language, or symbolization. By definition, the major side is the side governing symbols. In case of ambidexterity there may be a mixture. This is exemplified in an intensely interesting way by the case of Hermann and Pötzl.[2] Their patient showed the typical syndrome of Gerstmann with its accompanying disturbance of body scheme. The lesion was on the right side; this is not strange in view of the ambidexterity. However, the strange fact appears that the major and the minor side were apparently both on the right side of the brain. This is evident in the record of the authors, in which it is stated that localization of touch on the left became disturbed, most markedly in the forearm and hand. In their note of March 10 they stated that the patient deported himself as though he did not notice his left hand and foot. He was therefore unable to walk. Episodically, one could overcome the lack of use of the left hand by pointing out its presence, but he soon forgot the hand again. It "disappeared out of his spontaneity."

In this case one encounters both sets of symptoms from a lesion of the right side only. It would be interesting to speculate what a lesion of the left side would have done in this case.

Details of the physiology of the body scheme are not understood. It is indeed strange that on the minor side there should exist a group of cells the duty of which is to keep the opposite side of the body in the attention or in consciousness without a similar mechanism being present on the other side. Yet in every case of anosognosia reported to date the condition has resulted from a lesion of the right side of the brain. In every case of finger agnosia so far reported, except that of ambidexterity described by Herrmann and Pötzl, the lesion has been on the left side. Numerous cases have been studied in detail in which a lesion was observed on the left side in the same area which on the right would have caused amnesia or unconsciousness of the opposite side of the body; yet amnesia or unconsciousness of the right side did not result.

The report of a case in which this occurred follows:

CASE 8.—*Apoplectic onset of hemiplegia and homonymous hemianopia on the right; anosognosia of Babinski; delusion of absence of the right arm with gradual*

recovery of insight; agraphia; finger aphasia; constructive apraxia; allochiria; denial of paralysis and recovery from delusions, but not from paralysis.

Mrs. M. B., a white woman aged 57, was well until Nov. 10, 1936, when, on attempting to get out of bed in the morning, she fell and found that she was weak on the right side of the body. She was admitted to the hospital the same day and was examined by Dr. Ives who found a blood pressure of 190 systolic and 120 diastolic, marked arteriosclerosis, right hemiplegia including the face and tongue, right hemihypesthesia and right homonymous hemianopia. The deep reflexes were all increased, and there were Babinski and Hoffmann signs bilaterally.

Dr. Ives examined the patient for disturbance of body scheme on November 11, and I reviewed the case on November 12. The patient complained that her right arm felt "wrong" and related that on the preceding evening (the evening after development of the hemiplegia) she thought that some one else's arm was in bed with her and that her own arm was on the floor. She said: "Now that I see that it is my arm it must be, but it does not feel like it. I thought somebody was in bed with me, but I did not know who it was. I wondered if somebody was in bed with me with an arm across me." On questioning, she further explained that she had thought perhaps it was her daughter's arm, that she had come to stay with her but that she had not felt any portion of her daughter's body except the arm. At the time of examination she complained that her arm was water-logged and heavy and that the right leg "gets numb and kind of goes to sleep."

On further physical examination it was found that the sense of position was completely lost on the right side and that the patient was unaware of paralysis of the right leg, although she appreciated the weakness of the arm. She also showed allochiria and allachesthesia. Sensation at the right elbow was referred to the left forefinger, at the right thumb to the left fingers, at the right ankle to the left ankle and at the right toes to the left toes.

Examination for presence of the Gerstmann syndrome showed that the patient was unable to name her fingers (finger aphasia) but that she could demonstrate them correctly when asked. There was therefore no finger apraxia, and she was aware of their identity. On the other hand, there were a specific drawing defect and constructive apraxia. There was no alexia, the patient being able not only to utter words which she saw but to indicate their meanings. No form of visual agnosia was present. Neither was there any finger agnosia. However, she had complete agraphia and acopia.

Eight days from onset of the paralysis the patient had regained complete insight and explained that she had had a "hallucination" in the ambulance on the way to the hospital and thought that the arm was not hers. Seventeen days from the onset the hemiplegia remained unchanged, but the patient's mental state was normal.

Careful inquiry failed to reveal any history of left handedness in the patient or in any of her relatives or ancestors. Be that as it may, the patient undoubtedly had both the major and the minor area on the same side of the brain. The case was thus like that of Herrmann and Pötzl, except that the lesion was on the left side. The case demonstrates that delusion of absence of one side of the body is not confined absolutely to the left limbs. Like left handedness, the occurrence is not impossible, but is uncommon.

An explanation of the differences in disturbance of body scheme resulting from lesions of the two sides is desirable, but not yet available.

It seems possible that through phylogenetic training of the left side of the brain for finer differentiation, as for use of the fingers and symbolization, the cruder function has been abandoned.

In the field of cerebral localization great advances have been made during the last quarter of a century, much of which is not of aid in lesions of the right side. The syndrome of amnesia or unconsciousness for the left limbs stands out as one of the few definite aids in diagnosis of lesions of the right parietal lobe. On the left side the Gerstmann syndrome and its modifications have shed much light on localization of function in the parieto-occipital region.

ABSTRACT OF DISCUSSION

Dr. Israel S. Wechsler, New York: I was interested from a clinical point of view in the paper of Dr. Nielsen, which emphasizes the need for more accurate studies of aphasia. May I call attention to the fact that in finger agnosia, in which the patient cannot tell his fingers, there is no loss of primary modalities, whereas in astereognosis there is impairment in position sense and point discrimination?

In the body of the paper the author speaks of agraphia in addition to aphasia. It seems to me it is a part of aphasia, which is a generic term. Obviously, there are two kinds of agraphia: motor, or true, and ideational, or sensory, agraphia.

The question of how well one can localize a lesion by means of aphasia alone has always perplexed the clinician. It is extremely difficult unless one has additional evidence. For instance, if there are perceptive or sensory aphasia and, in addition, hemianopia, the localization becomes fairly accurate. Or if the language disturbance is more marked on the expressive side and there is a focal convulsion, one can point fairly well to the site of the lesion.

In my opinion, the tendency in recent years has been to oversimplify aphasia. This is a reaction to the armchair schematization to which studies of language were originally exposed. Many of the schemes simply did not exist. It seems to me that the paper by Dr. Nielsen points to the lack of wisdom in oversimplifying the whole subject of aphasia. Study of the Gerstmann syndrome shows the need for accurate and detailed analyses.

I was also much interested in the question of body amnesia. It is evident from the pathologic report that a lesion of the parietal lobe can cause this disturbance. I believe that Dr. Nielsen's paper is a fine demonstration of the possibility of accurate localization by means of detailed studies of agnosias and amnesias as parts of aphasia.

Dr. Richard M. Brickner, New York: It may be worth while to call attention to a relation between an observation by Dr. Nielsen and one by Head and Holmes. It brings into relief again the difference between the feeling-tone function of the thalamus and the intellectual, nonaffective function of the cortex. It also shows the similarity of the thalamus and the cortex in the localization in specific parts of the body of disturbances of feeling-tone, on one hand, and intellect on the other. I refer to the observation of Dr. Nielsen concerning absence of knowledge of the left side. In the cases of unilateral thalamus lesions reported by Head and Holmes, the side of the body opposite that of the lesion had pronounced changes in feeling-tone. They said:

"Music is peculiarly liable to evoke a different reaction on the two halves of the body. One of our patients was unable to go to his place of worship because

'he could not stand the hymns on the affected side,' and his son noticed that during the singing his father constantly rubbed the affected hand.

"A highly educated patient confessed that he had become more amorous since the attack, which had rendered the right half of his body more responsive to pleasant and unpleasant stimuli. 'I crave to place my right hand on the soft skin of a woman. It's my right hand that wants the consolation. I seem to crave for sympathy on my right side.' Finally, he added, 'My right hand seems to be more artistic.'

"The manifestation of this increased susceptibility to states of pleasure and pain is strictly unilateral."

It seems to me that these two observations, side by side, show clearly the difference, and the similarities, between cortical and thalamic function already alluded to.

Dr. J. M. Nielsen, Los Angeles: With regard to the agraphia being part of aphasia, that is undeniable. It is a fact that the agraphia in these cases is aphasic. There is another type which is due to apraxia, but that form is not under discussion. I purposely shied from the subject of aphasia as much as possible and laid stress on the three elements of Gerstmann's syndrome other than agraphia.

I think Dr. Wechsler is correct in using great caution in localization on the basis of aphasia alone.

With regard to amnesia resulting from a parietal lesion: I cannot explain that either. I know only that it occurs, and one sees patients who insist that one side of the body is absent. Sometimes the amnesia is only lack of focus of the attention. If one calls the patient's attention to the limb, he remembers, but in other cases no amount of calling attention and no quantity of evidence will convince the patient.

I have no personal acquaintance with the type of disturbance in the case mentioned by Dr. Brickner. At the hospital there is another series of cases in which there is a lesion affecting the thalamus, giving rise to the so-called anosognosia of Babinski, and the patient declares he is not paralyzed or is not blind or deaf, when he is.

I thought that was a separate subject, and I have omitted that group of cases.

Case Reports

NEUROMYELITIS OPTICA

With Pathologic Study in a Case

VERA B. DOLGOPOL, M.D., NEW YORK

The occurrence of optic neuritis with acute or subacute myelitis was mentioned for the first time in the literature by Albutt.[1] In discussing diseases, such as tabes and spinal injury, in which the spinal cord and optic nerves are affected simultaneously, he included an observation in an "unusual case" of subacute myelitis in which "sympathetic disorder of the eye appeared after subsidence of the acuter symptoms." Erb,[2] in describing a case of subacute myelitis associated with optic neuritis, was more emphatic in calling attention to this syndrome. Gault,[3] in a thesis written under the direction of Devic, collected from the literature seventeen cases of this syndrome (including one from the service of Devic) and gave the condition the name *neuromyélite optique*.

Neuromyelitis optica presents a characteristic clinical and pathologic picture; however, the identity of the syndrome as a clinical and pathologic entity has not been established.

As etiologic identification of the disease is impossible at present, anatomic study of clinically typical cases of neuromyelitis optica is the only method available for reaching a conclusion as to the nature of the disturbance and its status among other diseases of the central nervous system.

The number of cases of neuromyelitis optica studied both clinically and pathologically is not large. According to Salvati,[4] in 1931 pathologic examination had been made in only twenty-five cases of the syndrome, and few cases have been added since.

A patient with clinically typical neuromyelitis optica was observed in the service of Dr. Marcus Neustaedter at the Central Neurological Hospital, and pathologic study was made in the laboratories of that hospital.

REPORT OF CASE

History.—E. M., a West Indian Negress aged 35, single, a cook, was admitted to the Central Neurological Hospital on Sept. 20, 1932, complaining of inability to walk, numbness of the lower extremities and body from the waist down and incontinence of urine and feces. There was no history of familial disease. The

From the Pathologic Laboratories of the Central Neurological Hospital, Welfare Island.

1. Albutt, T. C.: On the Ophthalmoscopic Signs of Spinal Disease, Lancet **1**:76, 1870.

2. Erb, W.: Ueber das Zusammenvorkommen von Neuritis optica und Myelitis subacuta, Arch. f. Psychiat. **10**:146, 1880.

3. Gault, F.: De la neuromyélite optique aiguë, Thèse de Lyon, no. 981, 1894.

4. Salvati, G.: Neuromielite ottica, Arch. di ottal. **38**:310, 1931.

mother died in childbirth, and the father, of "fever," at the age of 59; a brother and a sister were well. The patient's previous illnesses were: trauma of the left eye in childhood, without impairment of vision, and a febrile disease, referred to as "grip," two weeks before onset of the present illness.

The present illness began sixteen months before admission to the hospital with numbness of the lower extremities, which extended gradually from the soles of the feet upward until it reached the waist-line. Two months after the onset the patient noted impairment of vision in the left eye and for a time had slight diplopia. A month later there developed unsteadiness of gait, with throwing out of the feet, and soon she was unable to stand or walk. Nine months after the onset she entered the Bellevue Hospital (in the service of Dr. Foster Kennedy), where there were found ankle and patellar clonus, slight exaggeration of the biceps and triceps reflexes and absence of abdominal reflexes. All forms of sensation were diminished or absent below the level of the tenth dorsal dermatome. Joint sense was absent below the hips. The visual fields were normal. Vision was 6/10 in the right eye and 4/10 in the left. The cerebrospinal fluid contained 20 cells per cubic millimeter (90 per cent of which were lymphocytes), with slight increase in globulin and normal dextrose content. The colloidal gold curve was 0112332100; the Wassermann reactions were negative with both the cerebrospinal fluid and the blood. The diagnosis was neuro-optic myelitis or tumor of the brain. The patient remained at the Bellevue Hospital for seven months, during which the status remained unchanged. She refused to undergo an exploratory operation and was transferred to the Central Neurological Hospital.

Examination.—In September 1932 Dr. Neustaedter reported that the sense of smell was normal. Vision was intact in the right eye and impaired in the left; the fundi were pale; the pupils were normal in size and reacted sluggishly to light and promptly in accommodation. The ocular movements were not impaired. All other cranial nerves were normal. There was no nystagmus and no exophthalmos. The patient was unable to stand or walk. Strength in the upper extremities was good and that of the abdominal musculature fair. Strength was poor in the lower extremities, the muscles of which were atrophic but showed no fibrillation. The finger to nose test was well executed; the heel to knee test could not be performed. Speech and handwriting were good. The pectoral, biceps, radial, triceps, ulnar, suprapatellar and patellar reflexes were moderately increased. The achilles reflex was present on the right and absent on the left. The Babinski reflex and confirmatory signs were present on the left, and the Chaddock reflex was elicited on the right. All abdominal reflexes were absent. There was a level of hypesthesia at the twelfth dorsal segment; temperature sense was diminished below the umbilicus, and vibratory sense, below the waist. Manometric values for the spinal fluid were normal. The colloidal gold curve was 1125554200. The Wassermann reactions of the blood and spinal fluid were negative. Examination of the blood showed no anemia.

Clinical Diagnosis.—In view of the sensory dissociation the diagnosis was syringomyelia.

Course.—Treatment consisted of massage and various thermotherapeutic procedures.

In September 1933, one year after admission, the abdominal reflexes were elicited, and the patient was able to move the legs slightly. In January 1934 examination showed pallor of both disks, more pronounced on the left, but no evidence of optic neuritis. The patient was able to move her toes and left leg. Control of the bladder had improved. All the abdominal reflexes were elicited.

The lower extremities showed spastic paraplegia, with a Babinski reflex bilaterally and other signs of lesion of the pyramidal tract. Pin-prick and touch were perceived throughout the body; vibratory sense, while present, was diminished. There was pronounced disturbance in the sense of position. The Wassermann reaction of the cerebrospinal fluid was again negative; the colloidal gold curve was 0111212110. The diagnosis made after this examination was chronic encephalomyelitis, with the maximal lesion in the spinal cord.

The condition remained essentially without change until October 1934, when vision became somewhat blurred, with slowly progressive impairment. Pallor of the disks was prominent.

In January 1935 the patient died of lobar pneumonia after a brief illness, three years and eight months after onset of the neurologic symptoms.

Necropsy.—As it was not expected that the body would be claimed and necropsy could not be performed until five days post mortem, a 20 per cent con-

Fig. 1.—Cervical intumescence, with loss of myelin in the lateral and posterior columns. Weigert-Pal stain; × 12.

centration of solution of formaldehyde U. S. P. (8 per cent formaldehyde) was injected into the cisterna magna after withdrawal of the cerebrospinal fluid (Dolgopol and Neustaedter [5]), in order to make possible microscopic examination of the central nervous system.

Gross Examination: The body was fairly well nourished. The skin showed no pressure sores. The corneas were cloudy (five days post mortem). The musculature of the upper extremities, abdomen and thighs was fairly well developed. The calves showed moderate atrophy; there was foot drop bilaterally. The spinal cord was uniformly well fixed with formaldehyde. The thoracic region of the cord was extremely thin, and no definite lumbar intumescence was

5. Dolgopol, V. B., and Neustaedter, M.: Cisternal Injection of Formalin for Fixation of the Brain in Delayed Autopsies, J. Tech. Methods **15**:33, 1936.

discernible. The brain weighed 1,260 Gm. and was fairly well fixed. The blood vessels at the base showed no sclerosis; the optic nerves were slightly flattened. On section of the brain, no softening or plaque formation was observed. Examination of the viscera showed lobar pneumonia involving the upper and lower lobes of the right lung, seropurulent pleuritis, degeneration of the myocardium, hyperplastic splenitis, chronic perihepatitis, acute hepatosis, acute nephrosis, subserous fibroma of the uterus, laceration of the cervix and chronic perisalpingitis.

Microscopic Examination of the Central Nervous System: Sections from the spinal cord, medulla, pons, cerebral hemispheres, cerebellum and optic nerves

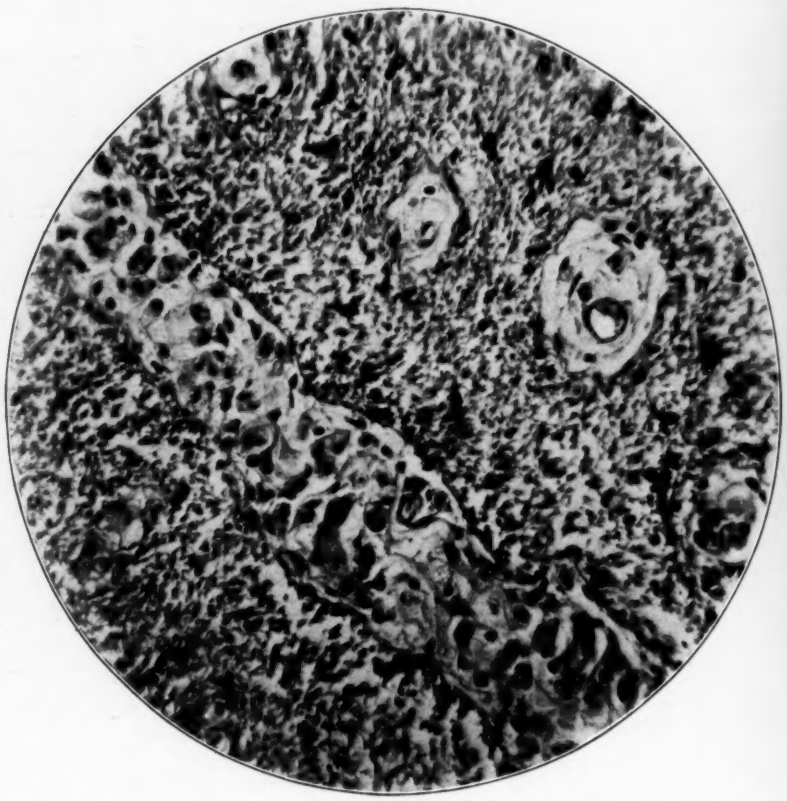

Fig. 2.—Thoracic portion of the cord, with perivascular collection of granular phagocytes in the lateral column. Hematoxylin and eosin; × 400.

were stained by the following means: hematoxylin and eosin, cresyl violet, the Weigert-Pal or the Spielmeyer stain for myelin, sudan IV for fat, the Hortega silver-lithium carbonate method for astrocytes, the method of Globus and Hortega for microglia and the Cajal reduced silver method for axis-cylinders.

Spinal Cord: Throughout the spinal cord the pia showed slight infiltration with lymphocytes, and small perivascular collections of lymphocytes were present in the anterior fissure. In the sacral region the myelin stain showed small triangular areas of demyelinization in the pyramidal tracts. In the lumbar region

extensive demyelinization was present in the crossed pyramidal tracts. In the thoracic region sections taken at several levels showed loss of myelin in the crossed pyramidal tracts, extending to the neighboring parts of the spinothalamic and spinocerebellar tracts; in the posterior columns there was loss of myelin in the columns of Goll and, to some extent, in the column of Burdach on the left. In the cervical region loss of myelin was observed in the crossed pyramidal tracts, in part of the posterior spinocerebellar tracts and in the columns of Goll (fig. 1).

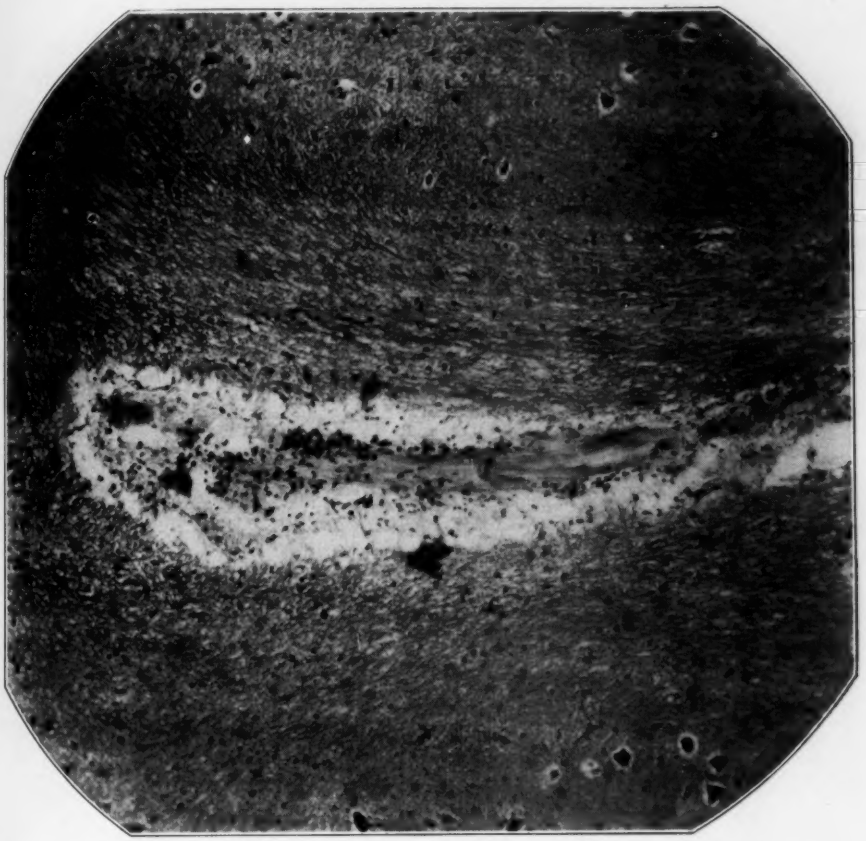

Fig. 3.—Medulla, with perivascular edema and collections of lymphocytes. Hematoxylin and eosin; × 150.

In sections stained with hematoxylin and eosin extensive increase in vascularity was observed in the lateral columns, the posterior horns and, at some levels, the posterior columns. The blood vessels (veins) were surrounded by wide cuffs of phagocytes filled with granular fatty material and by occasional lymphocytes (fig. 2). Giant astrocytes were seen in the lateral and posterior columns and in the posterior horns. Amyloid bodies were numerous in the posterior columns. The microglia was increased in the lateral columns, the posterior horns and the columns of Burdach. Some microglia cells contained from a few droplets to

large amounts of fat, so that transition to the fat-filled perivascular phagocytes was seen. Some fat-containing cells were located apparently within the lumen of the veins. The ganglion cells of the anterior horns contained much lipochrome, and some showed chromatolysis, especially in the thoracic region. The Cajal reduced silver stain showed irregular thickness and waviness of the axis-cylinders in the lateral and posterior columns, but there was no definite loss of these structures in the sections examined.

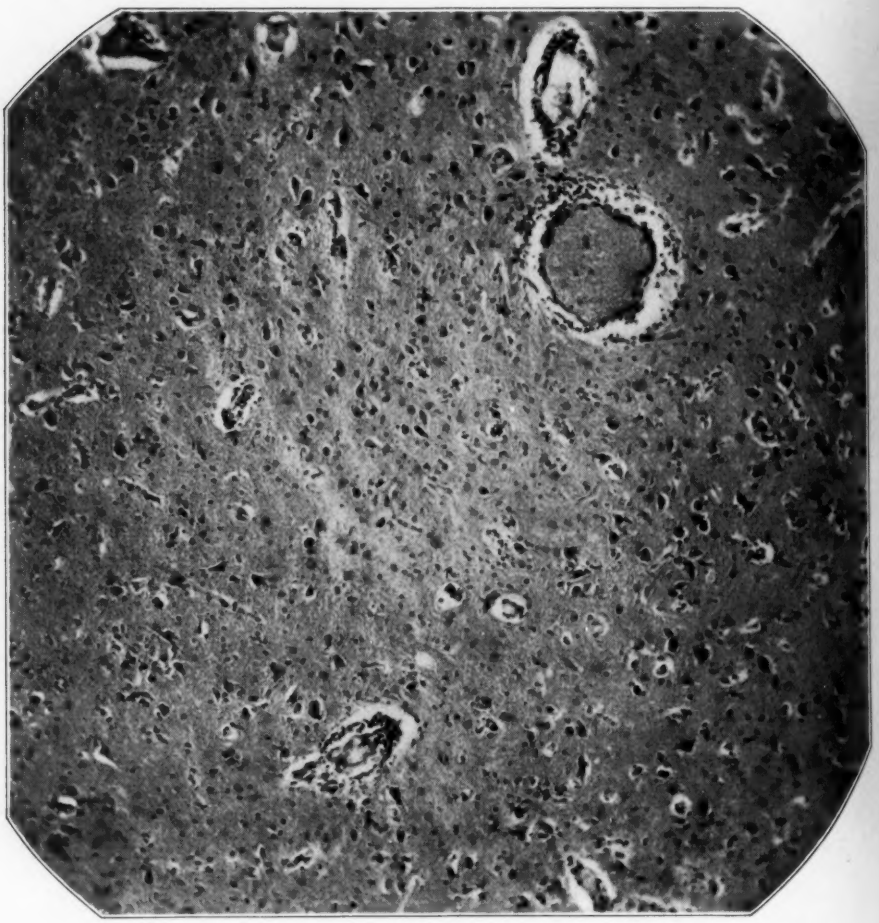

Fig. 4.—Claustrum, showing perivascular collections of lymphocytes. Hematoxylin and eosin, × 150.

Medulla: The medulla showed loss of myelin in the funiculus gracilis. A number of small veins with perivascular collections of lymphocytes and plasma cells were seen in the funiculus gracilis and funiculus cuneatus. Slight perivascular infiltration was present in the nucleus of the spinal tract of the fifth nerve and in the pyramidal tracts. Shrinkage of cells with diffuse staining or loss of

Nissl substance was observed in the nucleus funiculi cuneati and in the nuclei of the eleventh nerve. Extensive perivascular infiltrates were seen in the hili of the olives (fig. 3).

Pons: Several small arteries surrounded by a few lymphocytes and plasma cells were present in the meninges of the pons. The basilar artery was intact. No definite loss of myelin was seen in the pons.

Fig. 5.—Optic nerve, showing perivascular collections of lymphocytes and tortuosity of blood vessels. Hematoxylin and eosin; × 300.

Cerebrum: A few veins in the meninges were surrounded by a small number of lymphocytes. Acute toxic thrombosis was seen in several cortical veins, and perivascular edema was present around many blood vessels. The cortex showed a normal arrangement of cellular layers. The claustrum and external capsule on the right (fig. 4) showed a number of distended veins surrounded by several rows of lymphocytes; the surrounding tissue showed increased cellularity, apparently of microglial origin, and contained a large number of amyloid bodies. At

a level somewhat farther back, a granuloma-like nodule was present in the right peduncle; the nuclei were elongated and apparently belonged to microglia cells. The hippocampus showed no pathologic change. Small venules with a single row of lymphocytes were seen in the anterior part of the internal capsule, and below the thalamus; the cells of the nucleus ruber and substantia nigra were intact. Myelin stains of sections from the internal capsule and the cortex, including the occipital lobe, showed no patches of demyelinization; slight pallor was present only in areas of perivascular edema.

Cerebellum: A few veins with a single row of lymphocytes were seen in the meninges. The cerebellum was intact.

Optic Nerves (fig. 5): A number of tortuous veins were surrounded by lymphocytes. There was slight loss of myelin. The axis-cylinders were numerous throughout, but were rather thin in places.

Pathologic Diagnosis.—The pathologic diagnosis was disseminated encephalomyelitis with optic neuritis.

COMMENT AND SUMMARY

The clinical picture in the case described here corresponds essentially with that observed in cases of the condition described as neuromyelitis optica. The course of the illness differed in minor details from that in a typical case. The first manifestations, unlike the findings in the majority of cases, were sensory disturbances, followed in two months by impairment of vision; the motor disturbances developed only three months after the onset of illness. The fully developed clinical picture was that of retrobulbar neuritis and a spinal lesion of the transverse type, with the level first at the tenth dorsal and later at the twelfth dorsal dermatome, with dissociated sensory disturbances; abdominal reflexes were abolished; the reflexes of the upper extremities were increased, but coordination was good; speech was normal, and there was no nystagmus. After two years of illness some improvement was noted (slow restoration of some forms of sensibility, return of abdominal reflexes, better control of the sphincters and slight movements of the lower extremities). In the last months of life there was some subjective increase in visual disturbances. The patient died of lobar pneumonia, three years and eight months after onset of the neurologic symptoms. The cerebrospinal fluid showed a syphilitic colloidal gold curve. The Wassermann reactions of the spinal fluid and the blood were negative. The final clinical diagnosis was chronic encephalomyelitis, with maximal changes in the spinal cord.

Pathologic examination of the central nervous system showed loss of myelin in the crossed pyramidal tracts, with similar changes in the columns of Goll from the thoracic level of the cord up. There was no destruction of axis-cylinders; however, some were unevenly thickened and wavy, while others were thinner than normal. There was increase in the number of blood vessels in the lateral columns and the posterior horns, especially in the thoracic region; the blood vessels showed perivascular cuffing, consisting of phagocytes and lymphocytes. Perivascular infiltrations with lymphocytes were seen in the medulla, the claustrum and internal capsule on the right and beneath the thalamus (with the

nucleus ruber and substantia nigra intact). Occasional microglial rosettes were seen in the brain. There was no periventricular demyelinization in the cerebrum and no plaques in the cerebellum. The optic nerves showed perivascular infiltrations around tortuous blood vessels but no marked demyelinization or loss of axis-cylinders. The pathologic picture thus was that of disseminated encephalomyelitis and optic neuritis, with maximal lesions in the thoracic region of the cord. The degenerative changes were probably secondary to the inflammation.

Dr. Marcus Neustaedter permitted use of the clinical record of the patient, and Dr. Lewis Stevenson often gave advice in study of the case. Miss Rosa Bay-Ramyon prepared the histologic material, and Mrs. C. Watson made some of the photographs.

HEREDITARY CEREBELLAR ATAXIA

Report of a Case * and Genetic Study †

R. W. Waggoner, M.D., and K. Löwenberg, M.D., Ann Arbor, Mich., and Kathryn G. Speicher, Ph.D., Orono, Maine

There is no chapter of neurology and neuropathology which is more contradictory than that on the cerebellar ataxias. Strictly speaking, there are three types: (1) the heredocerebellar ataxia of Pierre Marie; (2) the olivopontocerebellar ataxia of Dejerine and Thomas, and (3) the ataxia with cerebellar cortical atrophy. The classification and differentiation of these conditions are difficult because the same parts of the brain stem and cerebellum are frequently affected. The most important property of Marie's type is its outspoken hereditary tendency. This property justifies its classification as a separate entity.

In this report we will consider only the hereditary form.

I. CLINICAL AND PATHOLOGIC STUDY

By Drs. Waggoner and Löwenberg

REPORT OF CASE

Well developed symptoms of the disease have been observed through five generations in 26 members of a white, American family of 180 members.

History.—P. M., a man aged 42, was first seen on Feb. 18, 1933. He complained of difficulty in talking of twelve years' duration and difficulty in walking of seven years' duration. He had contracted a chancroid at the age of 27 and was treated with silver arsphenamine. No clinical signs of syphilis were noted at the time of the examination.

The patient was a well built man, 170 cm. in height and weighing 75 Kg. Medical examination showed nothing abnormal. Neurologic examination revealed that the pupils were round and equal and reacted well to light and in accommodation. The eyegrounds were normal. There was no nystagmus. Speech was scanning, and there was a fine tremor of the tongue. The palate was high and arched. The biceps, triceps and radial reflexes were normal. The patellar and achilles reflexes were markedly diminished. The umbilical reflex was absent on

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* From the Neuropsychiatric Institute of the University of Michigan.

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the left and diminished on the right. There was marked ataxia of both the upper and the lower extremities; the patient walked with great difficulty on a wide base.

In August 1933 the patient's condition was much worse; he could not walk without support, and the ataxia was greatly increased. There was a Babinski sign bilaterally; both patellar reflexes were absent, and there was dysmetria on both sides of the body. The umbilical reflexes were present on both sides. The palpebral fissures were wide, showing sclera above the iris. The patient smiled in a childish way while attempting to perform coordination tests.

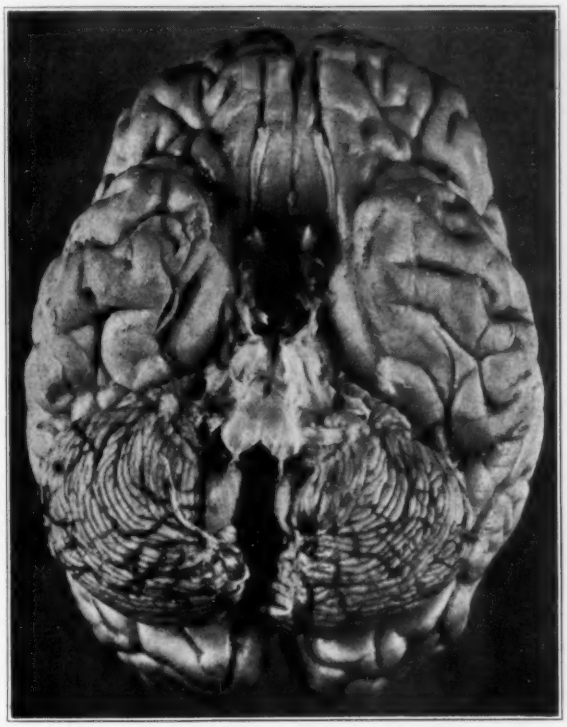

Fig. 1.—Moderate atrophy of both cerebellar lobes. Severe atrophy of the pons, both tonsils and the inferior vermis.

In the fall and winter the patient's condition became rapidly worse. After a fall, which resulted in a fracture of the right hip, pneumonia developed, and he died on Feb. 25, 1934, at the age of 43. The known duration of the disease was from fifteen to seventeen years.

Pathologic Observations.—Gross Changes: The pons and both brachia showed marked atrophy. The hemispheres of the cerebellum were moderately atrophic, except the tonsils, which were severely involved. There was distinct atrophy of the posterior vermis (fig. 1). The weight of the pons and cerebellum was 85 Gm., while that of the cerebrum was 1,125 Gm. The spinal cord, from the caudal parts of the olives to the cauda equina, did not appear grossly atrophic.

In frontal sections the fourth ventricle was greatly enlarged (fig. 2); the brachia conjunctiva were markedly atrophic and the roof nuclei were pushed rostrad and displaced. The dentate nuclei were narrow but distinctly visible (fig. 2). The white matter of the cerebellar hemispheres was slightly narrower than normal, and the gray folia were distinctly atrophic. The corpus restiforme (of which we were able to examine the rostral and caudal parts) was narrow on both sides. The olives (of which only the rostral and caudal parts were available) were poorly outlined. The basilar part of the pons was greatly atrophic.

The cerebral hemispheres and the basal ganglia appeared normal on gross examination.

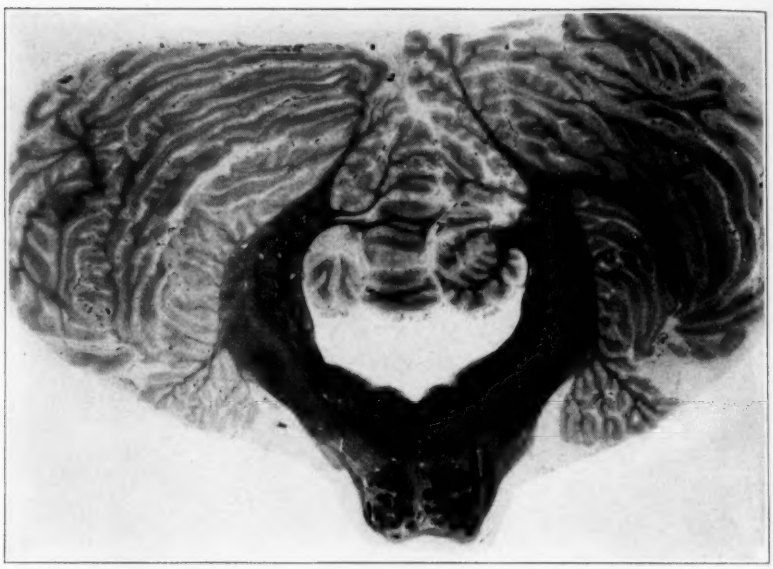

Fig. 2.—Section through the pons at the level of the nucleus of the sixth nerve and the cerebellum. The superficial and deep fibers of the pons (except several superficial fibers in the right side of the pons) are degenerated. The middle cerebellar peduncles and the cerebellar hemispheres are demyelinated. The outer fleece of the dentate nucleus is well preserved. The white matter of the hilus is narrow but is well stained. The fourth ventricle is greatly enlarged. Weigert stain; natural size.

Weigert Preparations: In the spinal cord, the fasciculus gracilis (Goll), fasciculus cuneatus (Burdach), fasciculus spinocerebellaris dorsalis (Flechsig) and fasciculus spinocerebellaris ventralis (Gowers) were involved.

The fasciculi gracilis and cuneatus were completely degenerated, while the fasciculi spinocerebellaris dorsalis and ventralis were less severely affected (fig. 3).

The pyramidal tracts, both direct and crossed, were well preserved. The fine myelin network of the gray substance of the spinal cord was greatly diminished. The neurons of the lateral and posterior horns and of Clarke's column were greatly reduced in number and in many areas were entirely destroyed. The motor neurons of the anterior horn were considerably reduced in number. The degeneration of the fasciculi affected the entire lower neuron.

The olives (including the dorsal and medial accessory olives) contained a few scattered neurons and a dense network of glia fibers. The olivocerebellar fibers, as well as the fibers of the hilus of the olives, were destroyed. The internal and external arcuate fibers had disappeared. The medial lemniscus and the reticulate substance were well preserved. Both the lateral and the medial part of the restiform body were demyelinated (fig. 4).

The brachium pontis (medial cerebellar peduncle) was greatly atrophic and demyelinated; its myelin stained grayish black, and the deep and superficial

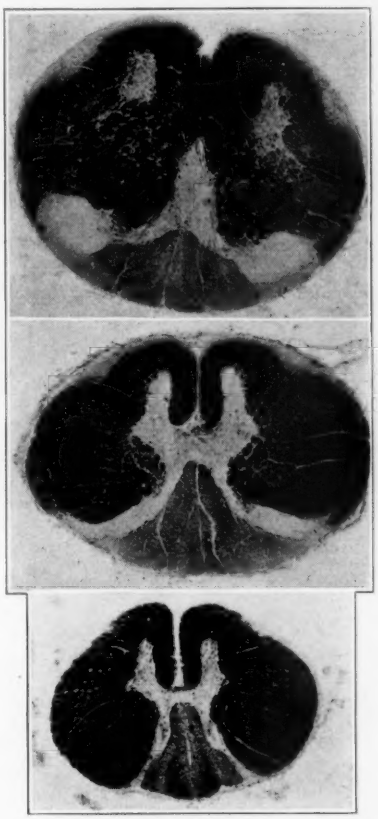

Fig. 3.—Photograph of three levels of the spinal cord with degeneration of the posterior and posterolateral tracts. Weigert stain; Zeiss planar 50 mm.

fibers of the pons had almost entirely disappeared. The raphe was demyelinated, and the neurons of the basilar part of the pons were almost completely atrophied (figs. 2 and 5). Microscopic examination revealed moderate degeneration of the sheaths, which were tortuous and broken in the areas described. The neurons of the pons, as seen in Nissl preparations, were reduced to a few scattered cells (fig. 5).

The myelo-architecture of the cerebellar hemispheres, the myelin of the folia and the central white matter of the hemispheres were greatly reduced, except for the flocculi, in which it was much better preserved. Here the architecture could

still be recognized, although the myelin network of all the plexus was considerably rarefied. In the cortex of the hemispheres the myelo-architecture was lost (figs. 2 and 6).

The anterior vermis was preserved, and the folia of the lobulus centralis contained more myelin than the folia of the hemispheres, while the amygdalae were entirely demyelinated.

Histologic Changes: The Purkinje elements and the neurons of the molecular layer were greatly reduced in number. There was a marked increase in glia fibers throughout the cerebellum (fig. 7).

The changes in the nuclei of the cerebellum were relatively mild. The nucleus dentatus was moderately shrunken, and its neurons were well preserved (figs. 2 and 8). The brachium conjunctivum was greatly atrophic and reduced to a narrow

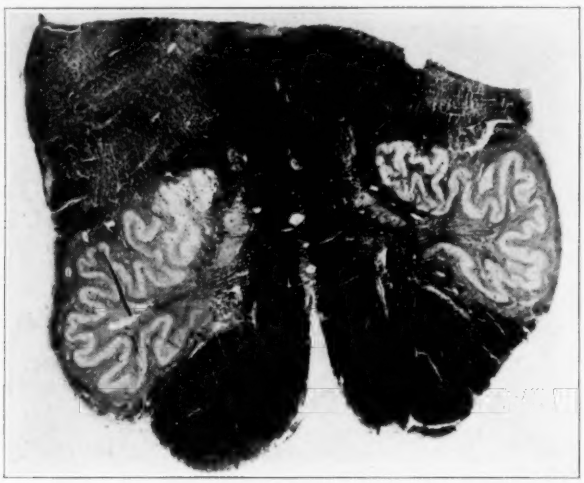

Fig. 4.—The olives are severely degenerated. Spielmeyer stain; Zeiss planar 50 mm.

band of fibers, which stained an intense black in Weigert sections (fig. 2). The internal, as well as the external, semicircular fibers were well preserved, but the adjacent parts of the restiform body were greatly reduced. The myelin fibers of the parenchyma of the dentate nucleus were greatly decreased in number. The parenchyma of the nucleus emboliformis, nucleus tecti and nucleus globosus was intact (fig. 8).

In the midbrain, the substantia nigra showed marked degeneration (fig. 9); the parenchyma of the red nucleus was moderately rarified, and the posterior quadrigeminal bodies were atrophic.

The hypothalamus, the basal ganglia and the hemispheres of the brain were normal.

There were: decrease in the size of the pons and cerebellum, and advanced degeneration of the white matter of the folia and of the deep white matter, the Purkinje elements and the granular layer of the cerebellum, the neurons of the pons, all three cerebellar peduncles, the olives, the olivocerebellar fibers, the external and internal arcuate

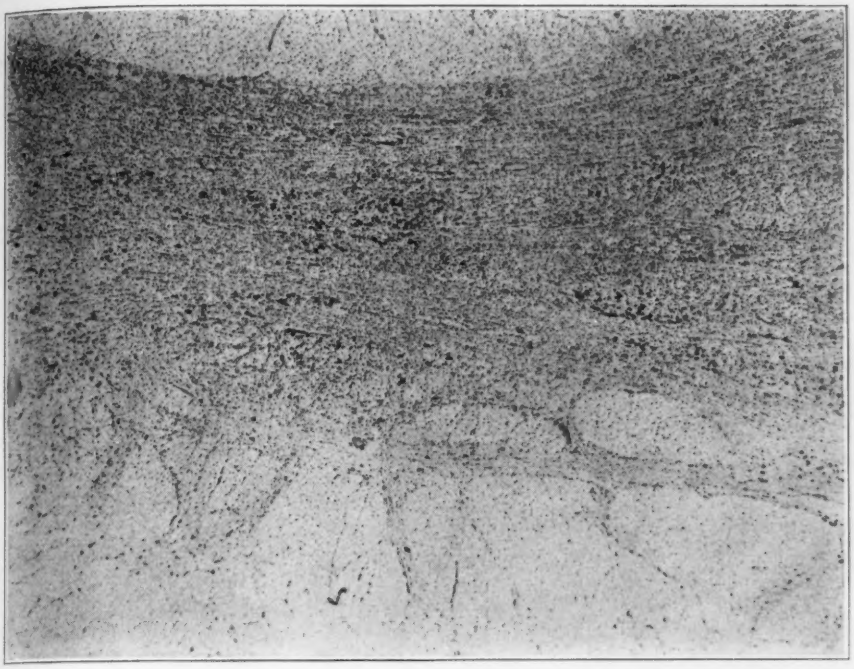

Fig. 5.—Photomicrograph of a section through the pons, demonstrating degeneration of the neurons of the pons. Nissl stain; Zeiss plantar 20 mm.

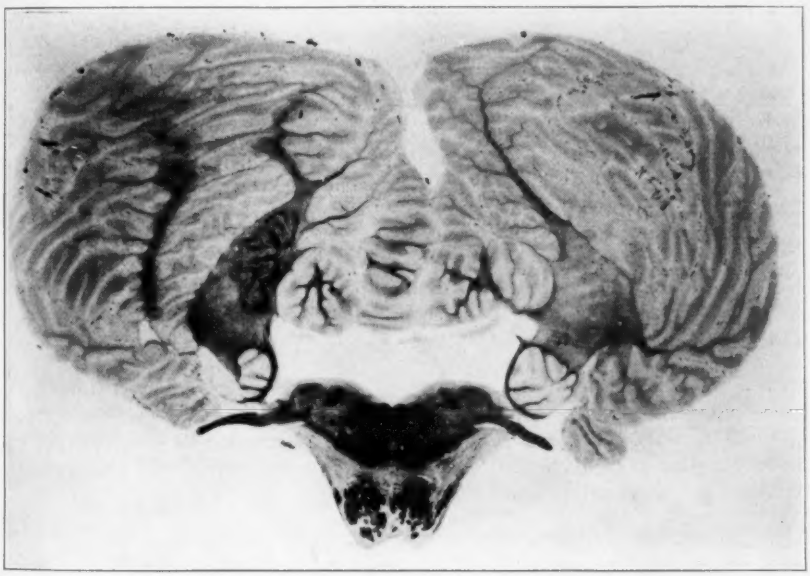

Fig. 6.—Photograph of a section through the region of the eighth nerve, demonstrating degeneration of the superficial and deep transverse fibers of the pons, the white matter of the cerebellar folia and the deep white matter of the cerebellum. The flocculus is relatively well preserved. Weigert stain; natural size.

fibers and the arcuate nuclei. In the spinal cord the fasciculi gracilis and cuneatus and, to a lesser degree, the fasciculi spinocerebellaris dorsalis and ventralis were degenerated.

COMMENT ON PATHOLOGIC MANIFESTATIONS

The pons, medulla and cerebellum have been described as atrophic in all the cases reported. The weight of the brain stem and cerebellum was 85 Gm. in our case, 120 Gm. in Nonne's [1] case, 81 Gm. in Fraser's,[2] 58 Gm. in Holmes,[3] and 57.7 Gm. in Bing's.[4] The weight of the entire

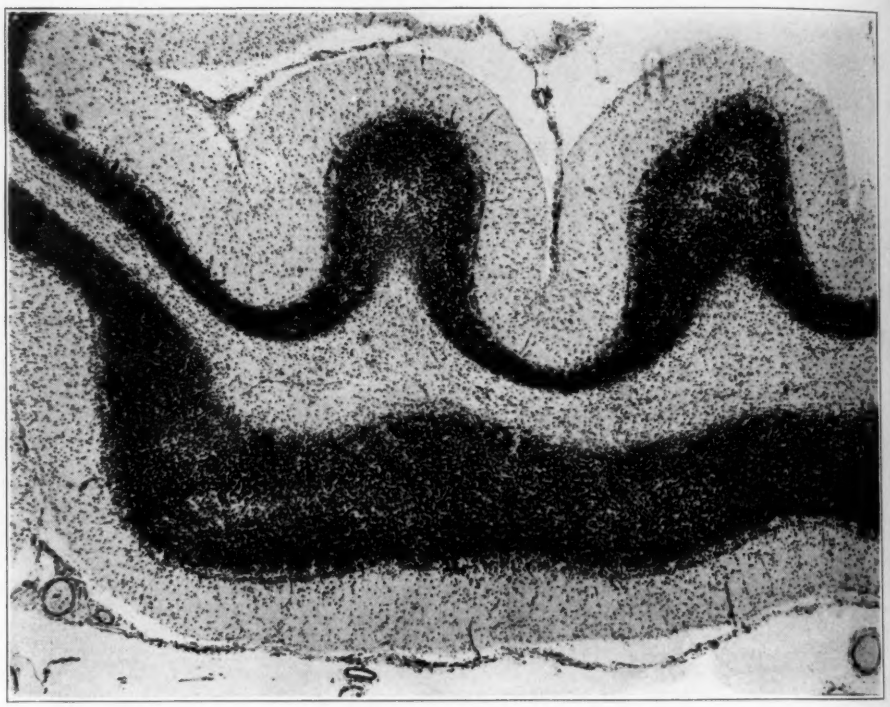

Fig. 7.—Photomicrograph of a section through the cerebellum. The Purkinje elements are greatly reduced in number; the granular layer is rarefied. Zeiss planar 20 mm.

central nervous system was reduced in some cases: 903.8 Gm. (Bing [4]) and 1,020 Gm. (Nonne [1]). Nonne compared the central nervous system in his case with that of a 10 year old child. Because of the atrophy of the cerebellar peduncles and the pons, the fourth ventricle was greatly enlarged in some cases (Menzel's [5] and ours).

1. Nonne, M.: Arch. f. Psychiat. **22**:283, 1891.
2. Fraser, D.: Glasgow M. J. **13**:199, 1880.
3. Holmes, G.: Brain **30**:466, 1907.
4. Bing, R.: Deutsches Arch. f. klin. Med. **83**:199, 1905.
5. Menzel, P.: Arch. f. Psychiat. **22**:160, 1891.

Patho-anatomic changes in hereditary cerebellar ataxias are otherwise variable. There is no system in the brain stem and cerebellum which is either always spared or always affected. The restiform body was involved in the majority of cases, but not in [illegible] Rydel [6] in 2 cases reported degeneration of the central part of this body, the area affected corresponding to the direct cerebellar tract. Barker [7] reported similar observations. In Rydel's [6] third case, in Hassin's [8] observation and in our case the olivopontocerebellar fibers were also degenerated. In Holmes' [3] observation the corpus restiforme was reduced to one half and in Menzel's [5] case to one fourth of its normal size, thus resembling the

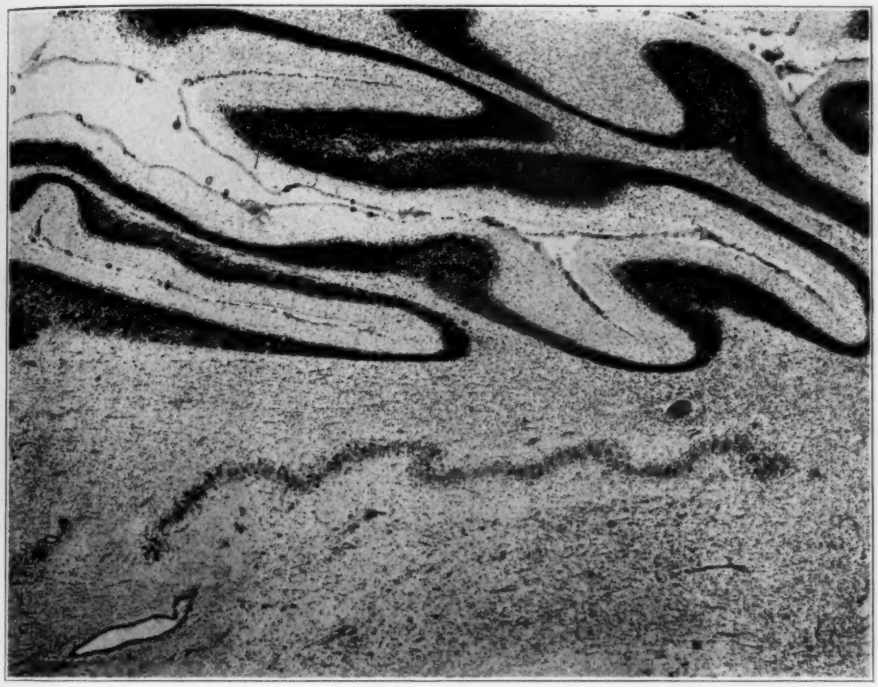

Fig. 8.—Photomicrograph of a section through the cortex of the cerebellum and the rostral part of the nucleus dentatus and nucleus emboliformis. The parenchyma of the nuclei is well preserved. Zeiss planar 20 mm.

changes in our case. On the contrary, Mathieu and Bertrand [9] observed only poor staining of the direct cerebellar tract, and Bing [4] found the corpus restiforme normal.

6. Rydel, A.: Nouv. iconog. de la Salpêtrière **17**:289, 1904.

7. Barker, I.: A Description of the Brains and Spinal Cords of Two Brothers Dead of Hereditary Ataxia, in Decennial Publications of the University of Chicago, Chicago, University of Chicago Press, 1903, vol. 10, p. 349.

8. Hassin, G. B., and Harris, T. H.: Olivopontocerebellar Atrophy, Arch. Neurol. & Psychiat. **35**:43 (Jan.) 1936.

9. Mathieu, P., and Bertrand, T.: Rev. neurol. **1**:721, 1929.

The olives were frequently, but not always, affected, and the degree of degeneration varied greatly. In the observations of Menzel,[5] Hänel and Bielschowsky,[10] Hassin [8] and Holmes [3] and in our case the olives were severely degenerated. Holmes [3] observed neurons only in the medial half of the ventral layer, where the cells were atrophic, loaded with yellow pigment and deficient in number. Mathieu and Bertrand [9] noted sclerosis only of the lateroventral part of the olives. In 1 of Rydel's [6] observations the olives were considerably affected, and in another, only moderately. Switalski,[11] Bing [4] and Barker [7] reported no changes.

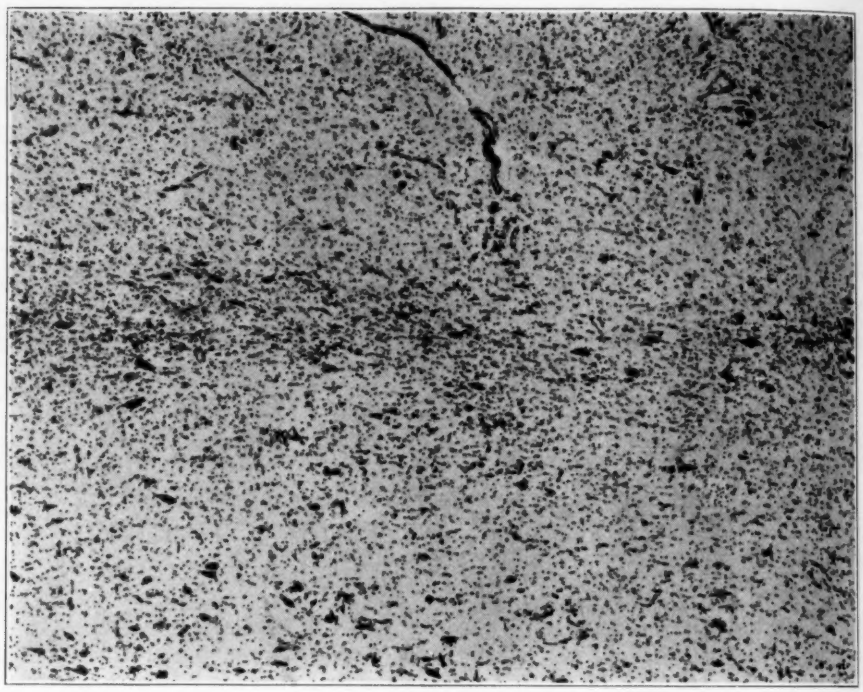

Fig. 9.—Photomicrograph of a section through the substantia nigra, showing advanced degeneration of the neurons. Nissl stain; Zeiss planar 20 mm.

The common observation of degeneration of the fasciculi gracilis and cuneatus and of their nuclei was made by Barker,[7] Rydel,[6] Menzel,[5] Bing [4] and us, and of the internal and external arcuate fibers and the arcuate nuclei, by Rydel,[6] Hassin,[8] Menzel [5] and us.

The middle cerebellar peduncles, the pons and its superficial and deep transverse fibers were atrophic in several cases (reported by Rydel,[6] Switalski,[11] Menzel [5] and Hassin [8] and us). Mathieu and Bertrand [9] observed, however, only partial destruction of the pons and peduncles, and, in Bing's [4] and Holmes' [3] cases both the middle peduncles and the transverse fibers of the pons were intact. Atrophy of the neurons of

10. Hänel, H., and Bielschowsky, M.: J. f. Psychol. u. Neurol. **21**:385, 1915.
11. Switalski: Nouv. iconog. de la Salpêtrière **14**:373, 1901.

the pons was reported in several cases. Severe atrophy was seen by Menzel,[5] Hassin [8] and us. In the observations of Mathieu and Bertrand,[9] Switalski [11] and Bing [4] the neurons were normal. Rydel [6] described a sclerotic lesion in the pons and in the medial, posterior and lateral walls of the fourth ventricle.

Changes in the cerebellum have been reported by the majority of authors. In the case reported here the hemispheres were moderately and evenly atrophied, but the inferior vermis was atrophic and the tonsils were greatly reduced in size. The flocculi were well preserved. Similar observations were reported by Mathieu and Bertrand [9] in their second case, in which the vermis was involved, while in their first case the cerebellum was small and the lamellae were atrophic. Considerable atrophy was also reported by Hassin,[8] Holmes,[3] Bing,[4] Switalski,[11] Rydel [6] and Hänel and Bielschowsky.[10] Quite different were the observations of Menzel;[5] the atrophy was restricted to the posterior semilunar and lunate lobes. The vermis and the flocculi were well preserved. Histologic changes in the cerebellum also vary greatly. Rydel [6] did not observe any deviation from normal; in Menzel's [5] case the granular layer was severely affected, and the Purkinje elements were destroyed. In the anterior vermis the changes were moderately severe, but the uvula and nodulus were normal. In our case the Purkinje elements were greatly reduced in number, and the granular layer was rarefied. Holmes [3] noted reduction of the molecular layer, great decrease in the Purkinje elements and some sclerosis of the granular layer. In Switalski's [11] case the granular layer and the Purkinje elements were normal.

The white matter of the hemispheres was affected in several cases. Menzel [5] noted that the white matter was greatly reduced, except for the vermis, which was better preserved, and the same was reported by Switalski,[11] who also observed atrophy of the right optic nerve. Holmes [3] found the white substance of the folia to be greatly reduced, especially in the superior vermis. Generalized reduction of the white matter associated with particularly severe demyelination of the flocculus was described by Bing,[4] while in our case there was generalized demyelination of the hemispheres associated with relative preservation of the flocculus. The outer fleece of the dentate nucleus was greatly rarefied, but the white matter of its hilus was well stained.

The nuclei of the cerebellum were relatively well preserved in the majority of cases. Advanced degeneration was reported only by Barker.[7] The changes were otherwise restricted to slight degeneration of the neurons associated with demyelination of the neuronal layer (in our case) and occasionally with that of the outer fleece. The brachia conjunctiva were affected in several cases (reported by Barker,[7] Mathieu and Bertrand,[9] Menzel [5] and us). Compensatory gliosis was frequent; hyaline degeneration of the vessels of the cerebellum was occasionally observed (Menzel [5]). Occasional formation of empty baskets and of climbing and mossy fibers was noted by Hassin.[8]

Finally, degeneration of the anterior quadrigeminal bodies was noted in Menzel's case,[5] of the posterior quadrigeminal bodies in our case and of the substantia nigra in both instances.

In the spinal cord there was marginal demyelination in the first case reported by Mathieu and Bertrand [9] and severe marginal degeneration in their second case. Rydel [6] reported degeneration of the tracts of

Gowers and Flechsig, and there were similar changes in Bing's [4] case. Barker [7] and we described severe degeneration of the fasciculi gracilis and cuneatus, and Hassin [8] reported mild degeneration of the posterolateral column and the posterior roots of the spinal cord. Degeneration of Clarke's column and of neurons of the posterior and anterior horns was frequently observed.

In reviewing the various and frequently contradictory patho-anatomic and histologic observations, one is compelled to conclude that the changes are nonsystemic and that there is no specific patho-anatomic picture in hereditary cerebellar ataxia. The opinion of Mathieu and Bertrand [9] that the pathologic picture in this condition is fairly characteristic cannot be confirmed. The best definition is still that of Marie,[12] who concluded:

> In heredocerebellar ataxia the atrophy involves all elements of the cerebellum in the gray and white matter. There is no lamellar involvement. The central nervous system is small, especially the pons and the inferior and superior peduncles.

This definition is sufficient so far as the gross changes are concerned. Marie's histologic definition,[12] in which he maintained that the histologic changes are comparatively insignificant, must be modified, as suggested by the review of the literature.

The patho-anatomic picture of heredo-ataxia resembles in some, but by no means in all, cases that of olivopontocerebellar atrophy, since in the former atrophy of the olives or of the pons, or even of the cerebellum, is not a constant factor.

The question arises whether it is possible to determine which part of the central nervous system is primarily involved. Hassin [8] assumed that the primary atrophy of the olives is followed by degeneration of other parts. It should, however, be borne in mind that in Rydel's,[6] Bing's [4] and Barker's [7] observations the olives were normal, while the cerebellum was severely affected. Furthermore, the primary destruction of the cerebellar cortex may be followed by secondary destruction of the contralateral olive (Schaffer [13]). It is far more likely that the atrophy of the olives in heredo-ataxia is secondary, as assumed by Marie,[12] Holmes [3] and Hänel and Bielschowsky.[10] It seems to us that the changes in the central nervous system at the time of death are too advanced to permit a decision as to the site of the primary atrophy.

COMMENT ON CLINICAL MANIFESTATIONS

Marie's heredocerebellar ataxia may occur at almost any age. In Bing's [4] case the first symptoms developed at the age of 5 years. In the 26 members of the family described here, the age of onset varied from 11 to 60 years. The disease may last for many years: in Bing's [4] case, thirty-seven years; in Holmes,[3] thirty-five years; in Menzel's,[5] from eighteen to twenty years, and in Switalski's,[11] seventeen years. The course may be progressive, or there may be remission for many years. In many cases the onset was gradual, consisting of progressive difficulty in walking, lancinating pains in the lower extremities and occasionally progressive ataxia of the upper extremities. Difficulties in speech were frequently noted. The patellar reflexes may remain normal, or they

12. Marie, P.; Foix, C., and Alajonine: Rev. neurol. **38**:849 and 1082, 1922.
13. Schaffer, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **30**:146, 1915.

may be hyperactive in the early stages, becoming diminished or lost as the disease progresses. Spasticity of the extremities has been reported in some cases. Disturbances of sensation are not uncommon. Choreiform movements, muscular hypertonicity, muscular twitchings and deformities of the spine and feet have been noted by some authors.

In general, it can be stated that the clinical picture varies greatly. Bing [4] found in his case no symptoms suggesting cerebellar disturbance, although patho-anatomically the cerebellum was greatly affected. Hänel and Bielschowsky [10] described convulsive attacks which occurred regularly when the patient was in bed, but no ataxia was noted.

We believe that it can be stated that, except for hereditary factors, there is no clinical or patho-anatomic syndrome of heredocerebellar ataxia as distinguished from those of olivopontocerebellar atrophy and cerebellar cortical atrophy.[14]

II. GENETIC STUDY

By Dr. Speicher

GENEALOGY

A study of the incidence and transmission of ataxia in the family to which P. M. belonged was made in Pennsylvania and Ohio in 1934, and data given are as of that year. The genealogy appears on the accompanying chart. Cases of ataxia, indicated by the black squares and circles, are numbered serially for purposes of reference, with numerals under the symbols.

The spread of the disease was traced among the descendants of the maternal grandmother of P. M., case 2. She, and also her father, case 1, are known to have been affected; her 4 siblings were reported to have been unaffected. Her descendants who lived to maturity or who are still living number 142 persons. The numerals above the symbols on the chart indicate the ages of living unaffected persons, only the upper and lower age limits being given in a family.

All children who died before reaching their majority are omitted from the chart because the late appearance of symptoms of the disease makes their inclusion of no value. The 35 children who now comprise generation VI, and whose ages range up to 14 years, have also been omitted, for the same reason. Of the 62 members of generation V, only the two families are shown in which cases of ataxia are already included. The ages of the 60 unaffected persons in this generation range from 3 weeks to 39 years. Diamond-shaped symbols are used in generations V to VI to represent as yet unaffected families of ataxic parents. The numerals in these symbols give the number of children; those above the symbols indicate the age of the oldest child.

DESCRIPTION OF CASES

As in family histories previously reported, there is here a characteristic clinical picture, probably dependent on the general hereditary background and modifying factors. Typical symptoms are: staggering gait, incoordination of movements of the hands, slurring speech, staring eyes, tremors, frequent choking, a tendency to cry, emaciation, absence of pain

14. The material for this study was contributed by the late Dr. Herman C. Stevens, Elyria, Ohio.

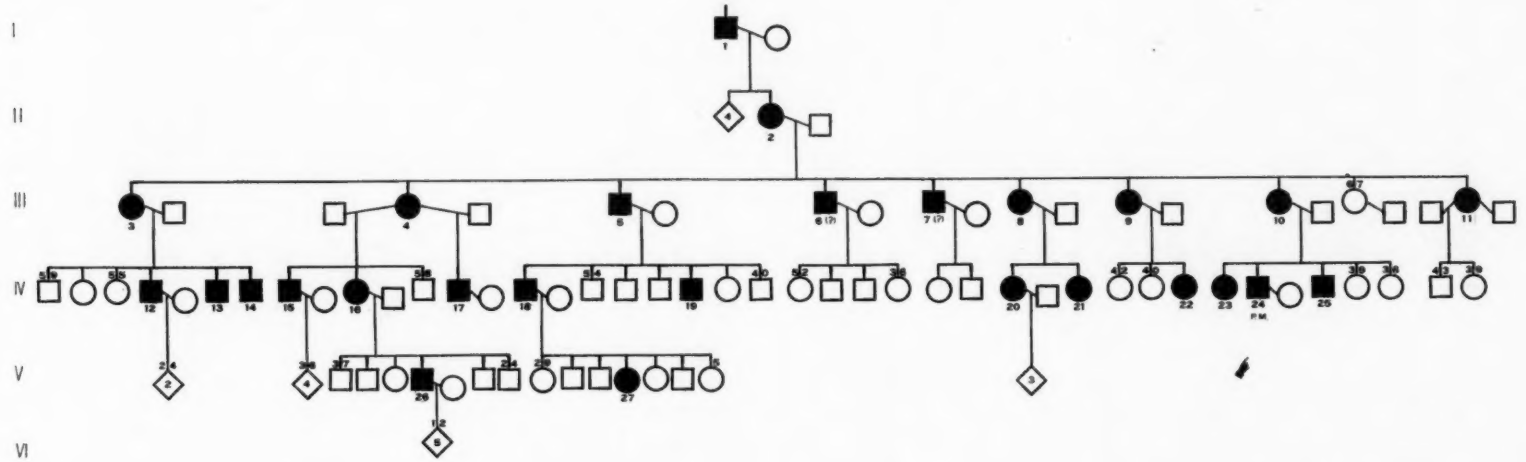

Fig. 10.—Genealogical chart of the five generations studied, of which our patient was a member of the fourth generation. The affected members are represented by black symbols.

and unimpaired mental faculties. Individual variations occur as might be expected; thus, the effect on speech was unusually severe in case 12, so that the patient could scarcely make himself understood; in case 19 a mental condition developed; control of the sphincters was lost in case 16; in both cases 17 and 27 tremors are exhibited, but in the former the head and hands are most involved, while in the latter there is jerking of the entire trunk.

The affected persons who have died lived from seven to twenty-five years after the onset, with an average of fifteen years. In 3 cases the patients failed to recover from falls, which occur frequently, owing to the ataxic gait. In 6 cases the family was not able to name any concomitant cause of death, but said merely that the patient died of ataxia.

Cases 6 and 7 are included because various persons interviewed independently declared that the disease was present, but they are considered dubious. In case 6 the patient lived to the age of 70; one sister denied that he had ataxia; two nieces independently reported him to be slightly affected, and his daughter said he "shook some." If ataxia was present, the onset was late, but no date for it could be established. The patient in case 7 is 76 years old. He lives in the state of Washington, and members of the family who were interviewed have not seen him for several years. They reported only that recently his handwriting has become scarcely legible and that he has given up driving his car. It is possible that in both these men there may have developed less severe nervous disorders concomitant with their advanced age, rather than ataxia. Their cases are interesting from the genetic point of view because ataxia has not yet appeared among their descendants. The first man had 4 children, ranging in age from 52 to 36 years, and 13 grandchildren, of ages from 27 to 3 years. The second has 2 children, whose ages are unknown but who are well above the threshold for the appearance of ataxic symptoms, and 2 grandchildren, 21 and 12 years of age. If the men mentioned were actually affected, they lived to be older than any other patient with the disease and displayed milder symptoms, which appeared at a more advanced age. Of persons with unquestionable cases the most similar is patient 11, who is now 66 years old and showed the first symptoms at the age of 60.

AGE OF ONSET

Kollewijn [15] described a family in which persons were affected with cerebellar ataxia after reaching the age of 70, while in a history reported by Blauner [16] children were involved. Both extremes are exceptional, as in the majority of cases reported symptoms have first been recognized at about the age of 30. In the present instance most of the cases have appeared in the decade of life between 27 and 37, with the modal age between 29 and 32. In the questionable cases 6 and 7 and in 4 well substantiated cases the disease appeared after the age of 37, and in 2 cases, before the age of 27. In the instances last mentioned, patient 13 showed symptoms of ataxia at the age of 21, and patient 27 is now 23 and was affected at the age of 16.

15. Kollewijn, J. R.: Nederl. tijdschr. v. geneesk. **2**:1225, 1917.

16. Blauner, S. A.: New York M. J. **100**:83, 1914.

A tendency for symptoms to appear earlier in succeeding generations has been described in cases of hereditary diseases that occur late in life. This progressive advance in onset has been called the "phenomenon of anticipation" and was applied to hereditary cerebellar ataxia by Sprawson,[17] in the case of an English family. It is now generally held that the "phenomenon" is only apparent and disappears when data are correctly interpreted, but an uncritical appraisal of this family history shows how readily such a conclusion may be made. The average age of onset in cases in which dates could be established was 43 years for generation III, and only 30 years for generation IV. Further, the 2 cases that have already appeared in generation V include case 27, in which there was the earliest onset yet recorded. The latter fact must, for the present, be accepted as fortuitous, as it will be thirty years before any general survey of generation V can be made. For the apparent discrepancy in the average age of onset between generations III and IV there are probably two causes. First, the oldest member of generation IV is still only 59, and a few cases appearing later than usual may yet raise the average age in that generation. Second, in the absence of clinical records, one relies for dates of onset only on the memory of individual persons, and most of those interviewed were members of generation IV, who may be expected to know the time of onset of ataxia in their own contemporaries more precisely than that in the parental generation.

GENETIC CONSIDERATIONS

The transmission of the disease in this family may be explained by assuming that it is governed by a single dominant hereditary factor. There is no evidence of sex linkage, as there would then be disparity in the sex ratio among affected children of ataxic males, and actually 2 sons and 2 daughters have inherited ataxia from their fathers. The trait is not sex limited, since it is as likely to appear in one sex as in the other. Of the 27 cases reported 13 are in females and 14 in males.

Dominance seems to be demonstrated unequivocally. No case occurs in which one of the parents was not known to be affected, and there are only 4 cases in which members of a family of an affected parent have passed the age of 30 without including a patient with ataxia. In 2 of these families are the descendants of patients 6 and 7, in whom the condition has already been mentioned as questionable because of the late onset and the mildness of symptoms. The other 2 are the small families of patients 11 and 15, in which the ages range from 43 to 25 and cases may yet develop.

Further, the 1:1 ratio of affected and unaffected persons to be expected from the operation of a dominant gene is approximated in generations in which it is already possible to number most of the cases. In generation II the incidence may be higher than that indicated on the chart, as lines from persons reported as unaffected were not followed. The ratio of affected and unaffected persons in generation III is disproportionately high (9:1), but would be lowered if patients 6 and 7 with questionable cases were really unaffected. Also, if these patients were free from ataxia, their 6 children in generation IV would be expected to be unaffected. There would then remain in generation IV 29 children of affected parents; among these 14 cases have already appeared. If, on the other hand, patients 6 and 7 were actually affected,

17. Sprawson, C. A.: Brit. M. J. **1**:23, 1914.

there would then be 35 children of affected parents in generation IV, with 14 affected and 21 unaffected. This is still not a wide departure from the expected ratio of 1 : 1 and, since no member of this generation has reached the age of 60 and there are still 4 unaffected persons less than 40 years old, additional cases are to be expected.

The dominance of the factor for ataxia in this family is in line with previous conclusions that the spinal ataxias are generally inherited as recessives and those of cerebellar origin as dominants. The consistent dominant behavior in this case makes it difficult to reconcile the findings with some of the theories previously formulated to fit less orthodox data. If one accepts Brain's [18] arbitrary scheme in which the appearance of ataxia depends on one dominant and one homozygous recessive factor, one must assume that the accessory recessive factor has a high incidence in the population of the region where this family lives. Again, if one follows Popenoe and Brousseau [19] in their theory that all hereditary ataxias are dependent on one and the same gene and that they vary in their genetic dominance as well as in their anatomic localization because of modifying factors, one may wonder at the consistency with which the trait acts as a dominant in this family, in which there is no consanguinity and modifying factors responsible for dominance might be expected to segregate from the main gene in a certain proportion of the crosses.

EUGENIC CONSIDERATIONS

Except for the ataxia, the stock in this family is good. Most of the members are apparently comfortably well to do and live in substantial homes. The men are farmers, professional men and, in some cases, day laborers. Their general attitude toward the transmission of ataxia varies between the extreme represented by the man who had five children after ataxia had developed and that in the case in which sterilization is known to have been resorted to when symptoms of ataxia appeared.

Outbreeding has not eliminated the taint in the family history as rapidly as might be expected. Theoretically, in every generation half the children of ataxic parents would be affected, so that in the first three generations descended from patient 2 incidences of 50, 25 and 12.5 per cent, respectively, might be expected. If one counts patients 6 and 7 as unaffected, the incidence in generation III is 70 per cent. In generation IV one-half the children of ataxic parents are affected and constitute 41.5 per cent of that generation, when 25 per cent would be the theoretical incidence. On the basis of cases which have appeared in generation IV and the present population of generation V, an incidence of 18.5 per cent can now be calculated for the latter generation, when 12.5 per cent would be the theoretical expectation. The excesses over the expected ratios are due to the high incidence in generation III and to the eugenically ironical fact that the one member of that generation who is to date unquestionably free from ataxia is the only one who has not left progeny. In generation IV, 7 of the 14 subjects were never married; 2 married after the ataxia developed but have had no children, and only 5 have left families.

Dr. Charles B. Davenport gave valuable advice and help, and the late Dr. Herman C. Stevens first examined patient P. M. and suggested this investigation.

18. Brain, W. Russell: Quart. J. Med. **18**:351, 1925.

19. Popenoe, P., and Brousseau, Kate: J. Hered. **23**:277, 1932.

DISCUSSION

DR. CHARLES DAVISON, New York: As Dr. Löwenberg has pointed out, one is confronted with the same problem in cerebellar diseases as in extrapyramidal disorders. After listening carefully to Dr. Löwenberg's clinical presentation and studying the slides that he has shown, I should like to ask him why he did not consider the disorder to be olivopontocerebellar atrophy. Truly, this condition is not an entity but a syndrome, as dystonia musculorum deformans is a syndrome of extrapyramidal disorders. Dr. Löwenberg did not mention whether the patient had atrophy of the optic nerve or ocular manifestations. In many cases of heredocerebellar ataxia these features are prominent and distinguish the condition from Friedreich's ataxia of olivopontocerebellar atrophy. The hereditary incidence should not rule out olivopontocerebellar atrophy, as in about half the cases reported this feature was shown.

Histopathologically, in the case described by Dr. Löwenberg and his colleagues, there was, in addition to involvement of the olivary, pontile and arcuate nuclei and cerebellum, degeneration of the dorsal columns. In a number of the cases reported in the literature the dorsal columns were involved. I am inclined to believe that olivopontocerebellar atrophy would be a more accurate term than heredocerebellar ataxia.

DR. K. LÖWENBERG: I stated that the disease was observed in five generations and showed an outspoken, dominant trend which so far has never been observed in connection with olivopontocerebellar atrophy, the latter being a sporadic disease. Thirty-two years ago certain authors had already complained that the conception of heredoataxia had become so hazy that it was impossible to understand what was meant by it. If all observations reported in the literature should be placed in a single group, a classification would be impossible. However, if one tries to get at the nucleus of the hereditary atrophy, a classification is, I think, not difficult. It is impossible to base a classification on the pathologic evidence alone; this is only a part of the clinical picture. Any classification must be based on genealogic, clinical and pathologic manifestations, and if that is done it is perfectly justifiable to assume that the ataxia of Pierre Marie is an independent disease.

TWO DAY CYCLES OF ALTERNATING GOOD AND BAD BEHAVIOR IN PSYCHOTIC PATIENTS

CURT P. RICHTER, PH.D., BALTIMORE

The first report that I have found of a case in which there were two or three day behavior cycles was made by Dömling,[1] of Würzburg, Bavaria, and published posthumously in 1804.

A woman aged 50 had been perfectly healthy up to her eighteenth year. Spells of dizziness which appeared at this time were treated with frequent bloodletting. She was married at the age of 21, and several pregnancies followed in rapid succession, with complications which were also treated with bloodletting. At the age of 33 blood was let from a vein under the tongue to relieve a severe toothache. The resulting bleeding could not be stopped for a long time, and, owing to the great loss of blood, the patient became weak and depressed.

Shortly afterward, cycles of two day duration made their appearance. On one day the patient was gay, and on the next she was depressed; her eyes were dull; her skin had a yellow-black color, and she complained of gastric pains. These cycles were present for fifteen years, with only occasional interruptions. The gastric pains, present on bad days, were treated with a wide assortment of remedies, including tinctures of camphor, naphtha, opium and ipecac, and even with animal magnetism. It was stated that a cure was finally achieved with large doses of opium and camphor. No details regarding physical examinations were given.

The next recorded case of two day cycles is that described by Oddo[2] in 1894.

The patient, who himself wrote a detailed account of his illness, was a French merchant more than 40 years of age. He had been healthy except for transitory attacks of rheumatism until the age of 35, when he began to feel bad and was easily fatigued. He became subject to mood swings of rather long duration. Three years later, after an attack of vertigo, he suddenly started to have mood swings of two days' duration. On good days he was cheerful, talkative, enterprising, full of ideas and not easily tired; on bad days he was discouraged and weak, had difficulty in thinking and was constantly overcome with sleep, in which he had nightmares. He was treated with quinine for a supposed atypical manifestation of intermittent malarial fever. The treatment had no effect. He complained of difficult breathing. The results of physical examination, if made, were not reported. The

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From the Psychobiological Laboratory, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital.

1. Dömling: Vermischte medizinisch-praktische Beobachtungen: Geschichte und Heilung einer sehr langwierigen periodischen und zwar dreitägigen Melancholie, Arch. f. med. Erfahr. **5**:1, 1804.

2. Oddo, C.: Neurasthénie circulaire: A forme alternante quotidienne, Rev. de méd., Paris **14**:603, 1894.

two day cycles had been present for two years at the time the report was made. They were regarded as manifestations of circular neurasthenia, which had been described shortly before by Sollier [3] (1893).

Dunin [4] reported the case of a man aged 87.

He had been normal and healthy up to the age of 79, when, owing to his negligence, he was faced with the problem of covering the financial losses of an institution of which he was manager. Marked dyspnea, present during a period of anxiety lasting a few hours, remained even when the danger of financial loss was shown to have passed. There was a recurrence of the attack within the following week. Cyclic variations in mood, which persisted uninterruptedly for eight years, started at that time. During the first three or four years a depressive phase lasting from twenty-four to thirty-six hours and a manic phase, lasting twelve hours, were followed by an interval of normal behavior, lasting a few days. Later, the normal phase dropped out, leaving only the depressive and manic phases, which had a total duration of from two to three days. On depressed days the patient was discouraged and hypochondriacal, concerned especially with disturbances of digestion and quite inactive; on excited days he was cheerful, contented and active. Physical examinations gave normal results.

Scheiber [5] reported the case of a German physician aged 63.

He had been entirely normal and had carried on an active practice until the age of 57. At this time an apoplectic attack occurred, immediately after a financial loss. There was no loss of consciousness, but after three days slight paralysis of the right foot remained. He suddenly became irritable, intolerant of contradiction and aggressive. An attack one year later was followed by the appearance of two day cyclic changes in behavior. On one day he was normal and cheerful; on the next he was irritable and elated, showed poor judgment and brooked no opposition. The fluctuations in mood between the two days became progressively more exaggerated with two later attacks. Bad days usually started promptly at midnight and lasted until the following midnight. On these days appetite was poor, and the patient complained of a peculiar taste in the mouth and markedly increased salivation. Physical examination gave normal results except for right hemiplegia, which had been brought on by a fourth attack resulting from arteriosclerosis. The diagnosis of manic-depressive psychosis was made.

MacLulich [6] reported the case of a woman aged 45 who had been in a depression for seven years.

The family history was without significance. A spinal deformity had appeared at the age of 16, and some time later the patient fell and struck the back of her head. Mentally she had been normal for twenty-two years, until the onset of the

3. Sollier, Paul: Sur une forme circulaire de neurasthénie, Rev. de méd., Paris **13**:1009, 1893.

4. Dunin, Theodor: Ueber periodische circuläre und alternirende Neurasthenie, Deutsche Ztschr. f. Nervenh. **13**:147, 1898.

5. Scheiber, S. H.: Ein Fall von 7 Jahre lang dauerndem circulärem Irresein mit täglich alternirendem Typus bei einem mit Apoplexie behafteten Individuum, nebst Bemerkungen zur sogenannten "circulären Neurasthenie," Arch. f. Psychiat. **34**:225, 1901.

6. MacLulich, P.: A Case of "Circular Insanity" in Which the Duration of Each Phase Exists for Only One Day, J. Ment. Sc. **45**:554, 1899.

psychosis, which was precipitated by her being frightened with a revolver. Her father had died some time before as the result of a revolver wound.

The chief feature of the psychosis was the two day cycle of depression and excitement. On depressed days she was listless and stuporous, avoided contacts, showed poor judgment and was untidy and destructive. On excited days she was confident, boasted about her figure and abilities, had visual and auditory hallucinations, thought she had all kinds of diseases and illnesses, talked incessantly and was incoherent and distractible. Her habits were clean, and she was not destructive. Memory for past events was good. The transition from one phase to the other occurred usually promptly and suddenly at about midnight. The diagnosis of circular insanity was made.

Ennen,[7] at the Psychiatrischer Verein der Rheinprovinz, in Bonn, Germany, reported two cases in which definite two day cyclic changes from mania to melancholia were shown (only an abstract was available).

In the first case, diagnosed as one of circular insanity, the disturbance started with a period of excitement and showed regular two day cycles for five years; in the other, of a similar psychosis, there were regular two day cycles for two years. No other details were given.

Ennen stated that in cases in which there are cyclic changes the disease is apt to have a prolonged course and an unfavorable outcome.

The patient reported on by Folin and Shaffer,[8] whose condition was diagnosed by Dr. August Hoch as a manic-depressive psychosis, was the subject of the only metabolic studies made in a case of two day cycles. The following description by Hoch is taken from the paper by Folin and Shaffer.[8]

"The patient's condition alternated with absolute regularity from day to day, being one day little removed from the normal, while quite disturbed on the other. These two states presented the following pictures: On the disturbed days the patient was often restless, walking aimlessly about with short steps, talking in the manner described below, or he handled things about him in an aimless way or took off his clothes, etc. His talk indicated that his ability to guide voluntarily his train of thought was much diminished. The different thoughts he uttered were but superficially connected, or his talk was constantly deflected by external happenings (great distractibility). Sometimes when less voluble he repeated the same question many times in a senseless manner or made remarks which were superficially suggested but which had no internal connection with what was spoken or what the circumstances demanded. Consequently when the abnormality was least marked, the main feature was a certain irrelevancy in the patient's remarks. The facial expression was almost always dull and immobile, the mood rather apathetic, but at times an irritability and occasionally a striking exhilaration were noted. He never lost his bearings, probably because the good days were constant correctives, but he had no clear appreciation of things or occurrences about him and on the good days he remembered poorly the sequence of events of the previous bad day. On the good days he often varied but little from the normal, but appeared somewhat

7. Ennen: Zur Lehre von den periodischen Geistesstörungen, Allg. Ztschr. f. Psychiat. **58**:1185, 1901.

8. Folin, Otto, and Shaffer, Philip A.: On Phosphate Metabolism, Am. J. Physiol. **7**:135, 1902.

dull without perfect appreciation of his condition and at times an irrelevant remark betrayed slight traits of the bad days."

The two day cycles in behavior in this case were observed for several months before Folin and Shaffer started their studies and for approximately one and a half years afterward. Nervous behavior usually started suddenly, between 10 and 11 a. m., and continued until evening. During the first year the cycles occurred with perfect regularity; later they disappeared and reappeared at irregular intervals; finally they disappeared altogether.

Chemical examination of the total output of urine showed two day cycles, particularly in phosphorus metabolism, corresponding with the behavior cycles. The phosphorus output was definitely increased on nervous days, especially in the afternoon, during the worst phase. The difference was most clearly expressed by the $\frac{100 \quad SO_3}{P_2 \quad O_5}$ ratio, which ranged from 62.5, on a good day, to 148, on a nervous day.

Differences due to fluctuations in food intake were ruled out by giving a uniform diet on good and bad days and by experiments with a normal subject as a control. A record of the $\frac{100 \quad SO_3}{P_2 \quad O_5}$ ratio while the patient was on a uniform diet is shown in figure 1.

Further observations made by Shaffer [9] and reported by him in a thesis submitted for the degree of doctor of philosophy in biochemistry at Harvard University showed that disappearance and reappearance of the cycles could regularly be predicted by precursory changes in phosphorus metabolism.

Folin and Shaffer offered the following explanation of this phenomenon:

"There exists in this patient on every second day a condition somewhat analogous to diabetes in virtue of which the system or some part of it is unable to assimilate (organize) a part of the phosphate absorbed from the digestive tract. The non-assimilated phosphate is eliminated on the same day, and the total amount of phosphate eliminated on the 'nervous' days is therefore greater than the amount eliminated by a normal person absorbing the same amount of phosphoric acid from the digestive tract. On the alternating days, on the contrary, a correspondingly less amount of phosphate than the normal is eliminated because on those days the system repairs the loss sustained on the preceding days."

Folin and Shaffer indicated also that changes in the phosphorus metabolism of nerve tissue may play a part in the production of these cycles.

It is possible that differences in activity, as well as in hours of sleep, may have been partly responsible for the differences in phosphorus metabolism. These factors were not controlled. The patient died about a year later, and a second diagnosis of dementia paralytica was made. The occurrence of similar cycles in many other patients in whom there could not have been any question of syphilitic condition eliminates syphilis in itself as a possible cause of the cycles in this patient.

Bleuler [10] described a patient with a lifelong tendency to depression and feelings of guilt.

A woman at the age of 48, one year after her husband's death, started to show alternate days of normal and abnormal behavior. On bad days she was negati-

9. Shaffer, Philip A.: Metabolism in the Insane: Analytical Technique, Thesis, Harvard University, 1904.

10. Bleuler, Eugen: Katatonie mit zweitägigem Zyklus, in Lehrbuch der Psychiatrie, ed. 2, Berlin, Julius Springer, 1918, p. 325.

vistic, rigid and depressed; on good days she was cheerful and cooperative. Except for a short period when a three day cycle was present, the two day cycle persisted without interruption for twelve years. Despite the almost constant presence of a depressive condition, Bleuler diagnosed the case as one of catatonia, apparently because of occasional hallucinatory experiences and catalepsy. No explanation was offered for the two day cycles.

Four cases from the Phipps Clinic, in which other features were shown, may be added to this collection. All four patients showed two day cyclic changes in behavior and sleep. Two showed the cycles in pulse rate also, and one, in body temperature. Unfortunately, at the time these records were collected all the patients had left the clinic. This explains the lack of many other examinations, particularly for phosphorus metabolism.

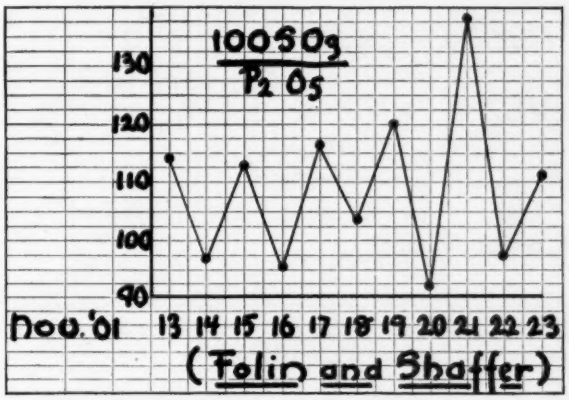


Fig. 1.—Daily records of the $\frac{100\ SO_3}{P_2\ O_5}$ ratio in the case of Folin and Shaffer, showing two day cycles.

REPORT OF CASES

Case 1.—Mrs. W., a housewife aged 59, was admitted to the clinic on two occasions with the diagnosis of a manic-depressive reaction. She had been subject to marked swings in mood, with the first depression at the age of 18. At the age of 45 she had a depression which lasted six months, during which she was self-accusatory and suicidal. Seven years later she fell into another depression, which lasted eighteen months. At the age of 57 she became irritable and hypomanic and then depressed and self-accusatory, with a fear of "going insane." When admitted to the clinic at this time, she was well oriented, but much depressed. She complained constantly of a peculiar taste in her mouth and of headache and inability to taste or smell certain foods. She worried unnecessarily about finances. Sleep was poor, but no sedatives were given. She showed gradual improvement and was discharged at the end of ten months. Two years later she was readmitted with the same features and was discharged after two years. She died at the age of 66, of cancer of the pancreas.

Her father had died in a state of depression, and a sister spent two months in a hospital with a depression.

Examination on admission to the clinic revealed slight obesity, moderate pyorrhea, slight increase in blood pressure (170 systolic and 79 diastolic) and hyperactivity of deep reflexes. Diabetes was present. During the patient's first stay at the Phipps Clinic, all her remaining teeth were removed, because of serious infection.

There were present definite two day cycles in behavior and sleep during the first five months of the patient's first hospitalization at the clinic. The pulse rate showed the cycles, but less regularly. On bad days the patient was sad and fearful; on good days, cheerful and active. Sleepless nights were followed by bad days and were often accompanied by an increase in pulse rate. A part of the record taken from the second month of the patient's stay in the clinic is presented in figure 2. It is a record of normal and abnormal behavior, hours of sleep and pulse

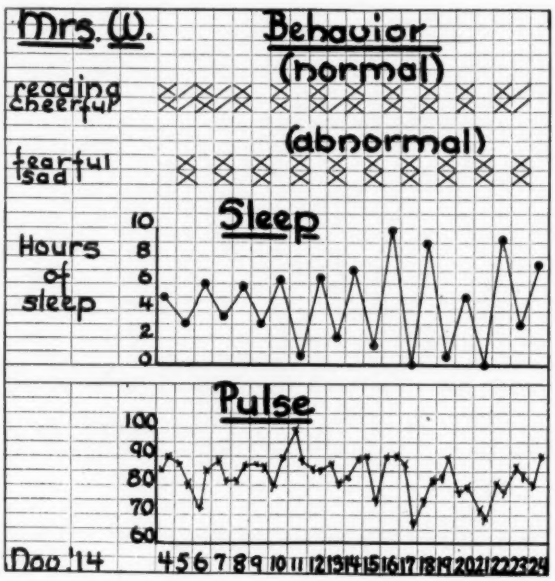


Fig. 2.—Daily records of behavior, sleep and pulse for Mrs. W., showing two day cycles.

rate. Sleep varied from none to ten hours, and the pulse rate from 66 to 100. On the patient's recovery the cycles in pulse rate disappeared first, then the cycles of sleep and finally those of behavior. At the end of nine months all three had disappeared. The infrequent appearance of the cycles during the next hospitalization may be explained by the almost daily use of sedatives.

The changes in behavior can be seen clearly in the following nurses' notes, taken from November 4 to 8.

November 4: Slept five hours. Had good night. Cheerful and quiet. Enthusiastic about her work. Made bed. Visited dressmaker in town. Ordered new suit. Walked back to hospital. Wrote letters in evening.

November 5: Slept three hours. Complained of noise during night. Much distressed. Upset because of purchase of suit yesterday. Many ailments during

morning. Slept one and a half hours after dinner, and again late in afternoon. Knitted late in evening.

November 6: Slept six hours. Awakened cheerful; very pleasant. Studied atlas. Ate well. Wrote letters after lunch. Went to market and bought fruit. Walked about the city for one hour. On return played bean-bag. Read aloud to other patients one-half hour. Had very good day.

November 7: Slept three and a half hours. Quite depressed. "I have been very selfish. I did as I pleased, and this is what it has brought me." "This every other day business makes me tired." "One day I am almost frisky; the next I am almost unbearable." Enjoyed gym and occupation work. Slept before and after lunch. Had to be urged to get up to walk.

November 8: Slept five and a half hours. Very cheerful. Did gymnastic exercises before breakfast. Blacked her own boots and helped make bed. Wrote several letters after breakfast. Busy all day knitting and writing. In late afternoon played bean-bag and went for long ride.

Case 2.—Mrs. B., a housewife, aged 60, was admitted to the clinic in 1915 with the diagnosis of agitated depression. She had always been sensitive, but amiable and cheerful and a good mixer. At the age of 56 a marked change in disposition occurred. She became seclusive and penurious, worried a great deal and lost weight. After the appearance of a cataract in one eye she became hostile to physicians, and it was necessary to send her to a sanatorium, where she stayed for three months, before coming to the Phipps Clinic.

Physical examination at the Phipps Clinic revealed pigmentation of the face and hands, slight enophthalmos, numbness of the right hand, fine but inconstant tremor of the hands, coarse tremor of the tongue, exaggeration of deep reflexes on the right side, benign tumor of the breast, enlargement of the liver and a urachal cyst.

During the first few months two day cycles were definitely present in behavior and sleep, and less regularly in pulse rate and temperature. They had been observed previously in the sanatorium. On bad days the patient was restless, dramatic, sarcastic and uncooperative; on good days, quiet and fairly cooperative. Bad days preceded by sleepless nights, were accompanied by an increase in pulse rate and body temperature. Variations in behavior on alternate days were so striking that on good days the patient became apprehensive about the next day and commented that the "change takes place in a few minutes and I am unable to explain it." She was also depressed about her behavior on the previous day. At times she breathed rapidly, complained of difficulty in breathing and swallowing and was often thirsty; on bad days she had a poor appetite. Part of the records for behavior, sleep, pulse rate and body temperature taken from the third month are shown in figure 3. Sleep varied from one to eight hours; the pulse rate, from 65 to 120 per minute, and the body temperature, from 95.5 to 99.3 F.

The alternation of behavior is demonstrated in detail in the following extracts from the nurses' notes, covering the period from May 16 to May 19 included in the charts in figure 3.

May 16: Ate breakfast; worked industriously on sewing all morning. Walked and sewed in afternoon; showed interest in people. Was quiet and agreeable before going to bed.

May 17: Slept only one hour. At 6 a. m. was confused and sarcastic. Would not eat breakfast. Restless, crying and agitated most of day. Ate little supper. Jumped up and down in bed.

May 18: Slept six and a half hours. Quiet; bathed and dressed. Acquiescent about everything. Read book. Watched ball game. Agreeable rest of day.

May 19: Slept three and a half hours. Confused at 6 a. m. Resistant about eating breakfast. Screamed loudly. Was sarcastic, imitative and argumentative. Fell on floor; rolled from side to side. Was put in dry pack at noon; talked constantly. Bit nurse. Spit on floor and bed. Went to bed quietly.

The cyclic changes were most marked during the third month of the patient's stay in the Phipps Clinic. They gradually disappeared, and after fifteen months, at the time of discharge, were present only occasionally. After seven years the

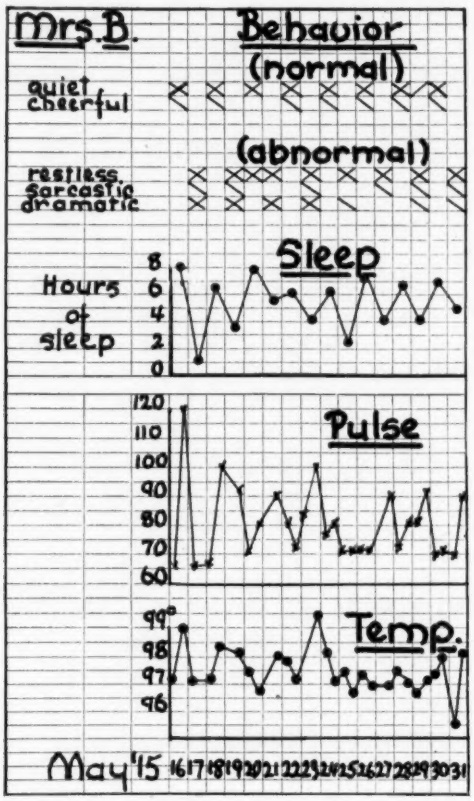


Fig. 3.—Daily records of behavior, sleep, pulse and temperature for Mrs. B., showing two day cycles.

patient was still at home and in fair health, except for occasional periods of worry and indecision.

Case 3.—Mrs. C., a housewife aged 45, was admitted to the clinic with a diagnosis of depression with hysterical and hypochondriacal features. Undisciplined and irresponsible, she never finished a whole year at school. She had whooping cough twice as a child and once at the age of 38. At the age of 25, she was unable to choose between marriage and staying with her mother, who was dying of an inoperable cancer. She went into a state of acute agitated depression. She

had sex fears and felt that marriage would be wicked. When she had recovered, she was married at the end of the year and was normal for three years. She then became overactive. Her sex life was unsatisfactory, and she grieved at remaining childless.

At the age of 43 she wrecked her car in an accident. She became more restless. At 44, while driving, she was in a collision in which a woman was killed; she felt she was responsible. Actually, a suit was pending. The menopause occurred at this time. She became more active, spent money recklessly and mishandled a trust estate for which she was trustee. She was finally placed in a sanatorium.

Physical examination revealed poor muscular tone, infection with Trichomonas vaginalis, relaxation of the sphincters, pyorrhea, hyperactivity of tendon reflexes, moderate coarse tremor of the hands, weakness on the left side of the palate and difficulty in swallowing. The chief complaints were blurring of vision, chronic constipation, nausea, inability to taste and smell, incontinence and insomnia.

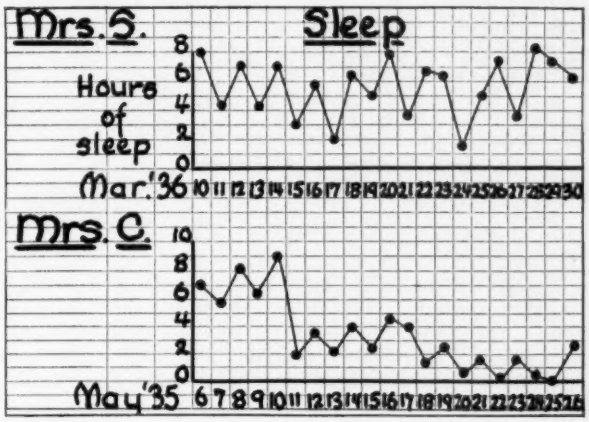


Fig. 4.—Daily records of sleep for Mrs. S. and Mrs. C., showing two day cycles.

While in a sanatorium, she showed alternation of good days, on which she was quiet and rational, and bad days, on which she exposed herself, was agitated, fearful, suicidal, uncooperative and worried about finances. During the first nine months in the Phipps Clinic, while sedatives were being given, cycles were irregularly present in sleep as well as in behavior. They were clearly present during the last three months, after sedatives were discontinued, and were still present for a month after the patient returned home. No cyclic changes were noted in the pulse rate or body temperature.

The cycles can be seen clearly in the record taken from the tenth month, that is, one and one-half months after sedatives were discontinued (fig. 4).

Case 4.—Mrs. S., a housewife aged 43, was admitted to the clinic with the diagnosis of depression with hypochondriasis. She was the youngest of eight children. She had very strict parents. She finished the seventh grade in school and went to work at the age of 13. She had always been timid, easily upset and perfectionistic. At the age of 29 she married her employer who was twenty years her senior. An unexpected and unwanted pregnancy six years later came as a great shock to the patient and her husband. There then began an intensive

worry about the child. At the age of 41, after complaint of gastro-intestinal disturbances, burning and severe pain in the abdomen, she was operated on for spastic colon. When no relief followed, she was given three cystoscopic treatments; later she was operated on for adhesions. She felt well for the next two and a half years. At the age of 44, when her son ran a knife through his fingers and was given antitoxin, all the symptoms reappeared. After two weeks in the hospital she underwent another operation for adhesions. She returned home in four weeks, and when symptoms reappeared she was admitted to the Phipps Clinic. She complained of weakness, palpitation, constipation, insomnia, pain in the abdomen and poor appetite. She had lost 20 pounds (9.1 Kg.) in the previous year. Her hands showed marked tremor. When freed from her somatic worries she improved rapidly, and after four months she was discharged as recovered.

During the first fifteen days of her stay in the clinic, when she received no sedatives, and also at frequent intervals during the rest of her stay she showed regular two day cycles, most clearly in sleep but also in behavior. A part of the sleep record is presented in figure 4. No cycles were present in the pulse rate or body temperature, although at various times both showed extremely wide fluctuations. On good days she was quiet, cooperative and cheerful; on bad days she was tearful and discouraged, but never violent or agitated.

COMMENT

In the absence of definite knowledge regarding their origin, cyclic changes in mood and behavior of psychotic patients have usually been grouped together as manifestations of a tendency to rhythmicity and as characteristics of manic-depressive psychoses. No attempt has been made to group them according to their different frequencies.

The results of studies of periodic phenomena in animals may throw a new light on the significance of these cycles. It has been shown that a number of cycles of different frequencies but of great regularity are present in the rat—some under normal conditions and some only after interference with one or another of the glands of internal secretion (Richter[11]). Regular hourly cycles of spontaneous activity were shown to be associated with hourly activity of the stomach; four to five day cycles of activity, with ovulation; fourteen day cycles, with disturbances produced by section of the pituitary stalk; twenty-five to thirty-five day cycles, with disturbances produced by thyroidectomy, and one hundred day cycles, with disturbances resulting from removal of one ovary and all except a small remnant of the other. The regularity of these cycles, particularly of the four to five day ovulation cycle, is almost perfect. Further experimentation will undoubtedly disclose many other cycles.

On the basis of this knowledge, it is believed that effort should be made also in the case of psychotic patients to group cycles according to their different frequencies, with the idea ultimately of using them to locate the organ or organs involved in the production of the psychotic disturbance.

In man it will not be possible to look for cycles of the same length as those found in rats. Human glands undoubtedly will be found to

11. Richter, C. P.: Animal Behavior and Internal Drives, Quart. Rev. Biol. **2**:307, 1927; Biological Approach to Manic Depressive Insanity, A. Research. Nerv. & Ment. Dis. Proc. **11**:611, 1930.

have other frequencies. For instance, the ovulation cycle in the rat is only from four to five days in length, while in man it is twenty-eight days.

Several definite cycles have already been reported (Richter [12] and Levine and Richter [13]). The two day cycle described here may now be added. Its origin is not known. The only other phenomenon known in man to have a two day frequency is the cycle of tertian malarial fever. It is doubtful whether malaria plays any part in this cycle, especially since Oddo found that treatment with quinine had no effect and no malarial organisms have been reported in the blood of any of the patients. It is most likely that these cycles are associated with some mechanism concerned with phosphorus metabolism, since the results of Folin and Shaffer demonstrated marked changes in output of phosphoric acid. The changes in taste also suggest a definite change in chemical metabolism of some kind. The disturbances in phosphorus metabolism point to the parathyroids, while the frequent occurrence of gastric disturbance combined with tremor suggests disturbance of the thyroid.

The relation of the two day to the one day cycle, the morning and evening variation, seen so often in cases of retarded depression, will be considered in a later paper. It is of interest that the changes in behavior of some of the patients with one day cycles are almost identical with those in the two day cycle described here. An interesting case of this kind was reported by Crichton.[14]

The significance of these cycles cannot be determined at present, in the absence of more data regarding the frequency of their occurrence in different types of psychoses. Undoubtedly, owing to extensive use of drug therapy in most institutions, many cyclic manifestations are blotted out.

On the basis of the present study, it is clear that two day cycles appear most frequently in patients with a manic-depressive history, are frequently precipitated by severe shock and in general have a long duration.

SUMMARY

1. Records of two day cycles in behavior, that is, alternation of one good and one bad day, were found in thirteen cases (nine from the literature and four new cases).

2. In general the patients were normal or elated on one day and depressed, agitated, combative or drowsy on the next.

3. The cycles were observed to recur with regularity for periods varying from several months to fifteen years.

4. The cycles may appear also in sleep—little or restless sleep preceding bad days. They may also be present in the pulse rate and body temperature.

12. Richter, C. P.: Cyclic Manifestations in the Sleep Curves of Psychotic Patients, Arch. Neurol. & Psychiat. **31**:149 (Jan.) 1934.

13. Levine, M., and Richter, C. P.: Periodic Attacks of Gastric Pain Accompanied with Marked Changes in Electrical Resistance of the Skin, Arch. Neurol. & Psychiat. **33**:1078 (May) 1935.

14. Crichton, John: Observations on Hydrophobia, Edinburgh M. & S. J. **31**:81, 1829.

5. All the patients (even the one diagnosed by Bleuler as having catatonia) showed definite manic-depressive symptoms.

6. In eight patients appearance of the cycles followed a severe shock or a period of mental strain.

7. The age at which the cycles were first noticed varied from 33 to 79 years. The average age was 50.

8. The duration of the illness of the patients was long in most instances.

9. The origin of the cycles is not known. The accompanying changes in phosphorus metabolism (increased output of phosphorus on nervous days) point to a chemical mechanism.

10. On the basis of observations made on the origin of cyclic changes in behavior of animals, it is likely that these cycles will be found to have origin in one of the glands of internal secretion, the function of which has been disturbed by age or some other factor. Establishment of normal function of the gland should eliminate the cycle as well as the accompanying changes in behavior, as it does in animals.

News and Comment

AMERICAN PHYSICIANS' ART ASSOCIATION EXHIBITION

The American Physicians' Art Association, a national organization of members of the medical profession who have ability in the fine arts, will hold its first national exhibition in the San Francisco Museum of Art in June 1938. (The Annual Session of the American Medical Association will be held from June 13 to 17 in the same city.)

The American Physicians' Art Association already has an outstanding membership. There are three classifications for membership: active, associate and contributing.

The first annual exhibition of the association promises to be of unusual interest, with entries to be accepted (after selection by a jury) in the following classes: oils, watercolors, sculpturing, photographs, pastels, etchings, crayon drawings, pen and ink drawings (including cartoons), wood carvings and book bindings. Scientific medical art work will not be accepted. The exhibition is not limited to first showings. All entries must be received by April 1. Any physician interested should communicate at once with the Secretary of the American Physicians' Art Association, Suite 521-536 Flood Building, San Francisco.

POSTGRADUATE INSTRUCTION IN NEUROPSYCHIATRY

The medical staff of the Menninger Clinic will conduct its fourth annual postgraduate course on neuropsychiatry in general practice from April 25 to 30, 1938, inclusive, at the Menninger Clinic, Topeka, Kan. The course will include a brief introduction to the fields of neurology and psychiatry and a specific application of this knowledge to the large group of psychoneuroses, psychoses and psychogenic and neurologic disorders which every physician meets in daily practice. The course has been planned to make it applicable to the common practical problems of the physician. An innovation will be group discussions of case histories and questions brought by members of the course.

CHILD NEUROLOGIC RESEARCH

The Council of Child Neurology Research announces that applications for grants will be considered at meetings to be held in April and October of each year. The purpose of the Council is to encourage original research on definite problems coming within the scope of child neurology and allied fields.

Applications must be in the hands of the Director, Dr. Bernard Sachs, 116 West 59th Street, New York, N. Y., before April 1 and September 15. The applicant must state distinctly the problem under investigation and the methods to be pursued.

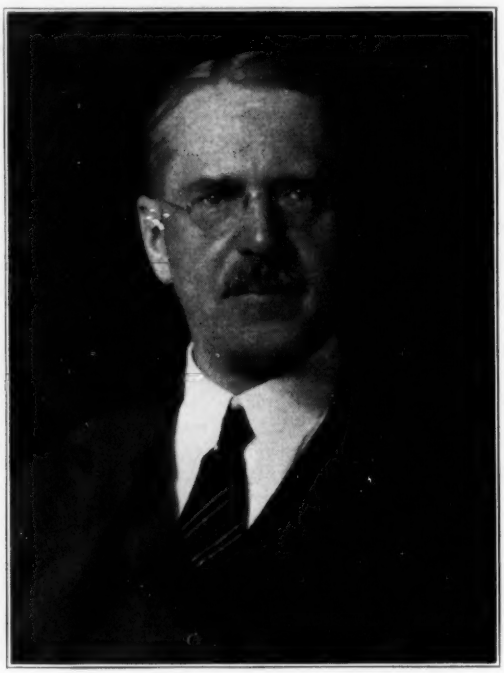
CONGRESS OF FRENCH ELECTRORADIOLOGISTS

The fourth annual congress of French-speaking electroradiologists will be held at the Faculty of Medicine of Paris, France, from Oct. 5 to 8, 1938. The program will include discussions on radiodiagnosis, the bioelectric phenomena of the nervous system, roentgenotherapy and physiobiology. Correspondence concerning the congress should be addressed to the president, Dr. Louis Delherm, 1 Rue Las Cases, Paris 7e.

Obituary

JAMES RAMSAY HUNT, M.D.
1872–1937

James Ramsay Hunt had an international reputation for his knowledge of the physiology and the medical aspects of the nervous system. His keen clinical observation brought to light several conditions previously unrecognized. His researches on paralysis agitans did much to reveal the structure and function of the basal ganglia of the brain, about which, before his work, little was known. He was a man unas-



JAMES RAMSAY HUNT, M.D.
1872-1937

suming, of great natural dignity and most whimsical humor. His great stature, the slow rhythm of his movements and the mien of dignity of which I have spoken made me once say to him, as we were laughing together, that if I were restricted to a single adjective with which to describe him I should choose "Olympian."

He endured a protracted and painful illness with a stoic calm, gentled by philosophic humor, bearing the curse that most doctors must bear at the end, of knowing the ultimate result of his condition. He had, indeed, malice for none and charity for all. His gentle chaff of the foolish hurt none and bettered many. There was in his life and work and bearing fine distinction. He was a great American gentleman.

Abstracts from Current Literature

Anatomy and Embryology

AN EXPERIMENTAL STUDY OF THE ORIGIN OF THE CELLS WHICH CONSTITUTE THE SEVENTH AND EIGHTH CRANIAL GANGLIA AND NERVES IN THE EMBRYO OF AMBLYSTOMA PUNCTATUM. C. L. YNTEMA, J. Exper. Zoöl. **75**:75 (Jan.) 1937.

Ectoderm of the neural crest, the auditory placode, the preauditory placode or the hyomandibular epibranchial placode, or a combination of these rudiments, was transplanted to the host in the orthotopic position in Amblystoma embryos (stages 15 to 30). About two hundred and fifty animals between stage 30 and the 3 cm. larva stage were studied. By staining either the host or the grafted tissue at the time of operation with nile blue sulfate, the contributions of each could be differentiated. Four sources of the immature acousticofacial complex were determined: The primitive root is derived from the neural crest; the lateral seventh ganglion, from the preauditory placode; the visceral seventh ganglion, from the hyomandibular epibranchial placode, and the eighth ganglion, from the auditory vesicle. The neurons of the complex arise from placodal ectoderm. The visceral sensory neurons are derived from the epibranchial placode, the special somatic sensory neurons from the dorsolateral placode, the acoustic neurons from the auditory vesicle and the lateral line neurons from the preauditory placode. At least part of the satellite cells have a placodal origin, in common with their neurons. Sheath cells of the seventh and eighth nerves arise from the neural crest and the dorsolateral placode. The origin of the buccal ganglia from placodal ectoderm was also demonstrated.

WYMAN, Boston.

EXPERIMENTAL STUDIES ON THE DEVELOPMENT OF THE EYE: IV. THE EFFECT OF THE PARTIAL AND COMPLETE EXCISION OF THE PRECHORDAL SUBSTRATE ON THE DEVELOPMENT OF THE EYES OF AMBLYSTOMA PUNCTATUM. HOWARD B. ADELMANN, J. Exper. Zoöl. **75**:199 (Feb.) 1937.

The neural plate was turned back, and portions or the whole of the prechordal substrate was removed in embryos of Amblystoma punctatum in the early neural plate stage (between stages 14 and 15). The animals were killed and sectioned at various stages thereafter. Unilateral extirpation of the "mandibular" portion of the substrate resulted in reduction in size of the mesodermal muscle mass of the mandibular arch on the side of operation. Marked decrease in the muscle was accompanied by reduction in the size of the eye on the same side. When the prechordal plate was excised as well, the muscle mass of the mandibular arch was absent or severely reduced. Twelve of sixteen of these animals exhibited various degrees of synophthalmia or cyclopia, and in half of them the forebrain was typically cyclopean and related to a single olfactory placode or sac. Excision of the entire prechordal substrate had no more serious results than extirpation of the prechordal plate together with the "mandibular" portion of one side only. Synophthalmia or cyclopia resulted from the ventrolateral evagination of the entire optico-ocular apparatus. The materials which normally expand to form the primitive chiasm were left intact. The results indicate that the prechordal substrate first determines a generalized "field" for the eye and forebrain and that within this territory the prechordal plate effects the proper bilateral massing of these materials.

WYMAN, Boston.

THE ADRENAL-AUTONOMIC COMPLEX IN ALLIGATOR MISSISSIPPIENSIS. FLORENCE EMILY LAWTON, J. Morphol. **60**:361 (March) 1937.

Since virtually no previous work had been done on the adrenal-autonomic system in reptiles, this complex was studied in Alligator mississippiensis. Young animals, from 25 to 35 cm. long, were used for the gross anatomic studies, and embryos, from 6 to 20 mm., for the microscopic. The adrenal bodies are distinct from the kidney, lying against the wall of the inferior vena cava and, in young animals, close to the gonads. Cortical cells predominate. In embryos the medullary tissue is not dispersed, as in older animals, and lies close to the blood sinuses or surrounds them. The arterial supply is scanty, but the supply from the inferior vena cava is profuse. In addition, there are three small veins from the body wall. The nerve supply is segmental, four or five consecutive sympathetic ganglia sending sympathetic nerves to the adrenal. A parasympathetic innervation was not observed. A sympathetic nerve often branches two or three times as it leaves the ganglion and proceeds to the medullary portion of the gland, where its sheaths are lost. The innervation suggests transition from lower forms, with segmental, diffuse medullary tissue, to higher forms, with concentration of nerve supply and adrenal tissue.

WYMAN, Boston.

THE THALAMUS IN RELATION TO THE CEREBRAL CORTEX. EARL WALKER, J. Nerv. & Ment. Dis. **85**:249 (March) 1937.

A general survey of the thalamus suggests that it may be divided into three groups of nuclei. The first includes the nuclei having entirely subcortical connections concerned either with a phylogenetically old system, the nuclei of the midline and the nucleus ventralis anterior, or, probably, with intrathalamic associations. The second group, the nucleus ventralis lateralis, the nucleus ventralis posterior, the anterior nuclei and the geniculate bodies, consists of nuclei receiving fibers from the ascending sensory tracts and projecting to the cerebral cortex. The third group, the nucleus medialis dorsalis, nucleus lateralis posterior and pulvinar, receive no fibers from the great ascending pathways but have numerous connections with the thalamic nuclei of the second group and project to the associative areas of the cerebral cortex, whereas the fibers of the second group end in the projection centers of the cerebral cortex.

Study of the connections of the cortical areas gives further evidence for the concept that at least a partial synthesis occurs in the nuclei of the third group. The prefrontal area receives fibers from only the adjacent motor areas (areas 4 and 6 of Brodmann) and sends fibers to the latter region and to the parietal cortex. Certainly, the fact that the prefrontal cortex has so few connections and yet unquestionably plays a large associative role, as determined by psychologic tests, points to the fact that the subcortical connections relay at least partially synthesized impulses from the thalamus. The parietal cortex (areas 5 and 7) has a much larger associative field—the prefrontal area and the precentral and postcentral convolutions, as well as the periparastriate areas and the temporal cortex. The periparastriate areas likewise have a wide associative field, particularly with the striate cortex. It is probable that the thalamic projections to these areas, having such wide cortical connections, must be of a fairly high functional order.

The thalamus, then, may be considered as a great subcortical receiving station where incoming impulses are relayed to the primary projection centers, or integrated to a greater or less extent and then transmitted to functionally higher cortical centers.

HART, New York.

Physiology and Biochemistry

THE RELATION OF THE POSTERIOR PITUITARY TO WATER EXCHANGE IN THE CAT. W. R. INGRAM and C. FISHER, Anat. Rec. **66**:271 (Oct.) 1936.

Total removal of the pituitary stalk or of the stalk plus the posterior lobe in cats resulted in permanent diabetes insipidus provided a portion of the anterior

lobe remained. The supra-optic nuclei and any remaining portions of the posterior lobe were degenerated in these cases. Almost complete removal of the posterior lobe or partial section of the stalk was not followed by polyuria. The presence or absence of the pars tuberalis did not affect the results.

RIOCH, Boston.

THE PHOSPHOLIPID METABOLISM OF TUMORS. FRANCES L. HAVEN, J. Biol. Chem. **118**:111, 1937.

The purpose of this investigation was to ascertain whether the phosphatides present in rat carcinosarcoma undergo rapid catabolism. Elaidin, which is the glyceride of elaidic acid, was fed to rats with tumors, and the amount of elaidic acid which had been taken up by the phosphatides in the tumors was determined. It was found that only about one fifth of the fatty acids present in the phosphatides was elaidic acid. Furthermore, the rate of entrance of elaidic acid into and disappearance from the tumor phosphatides was slow as compared with that in the liver. It is Haven's opinion that these results indicate that tumor phosphatides are concerned with the structure of cells rather than with the burning of fatty acids to yield energy.

PAGE, Indianapolis.

EVIDENCE OF SELECTION IN THE BUILDING UP OF BRAIN LECITHINS AND CEPHALINS. KENNETH P. MCCONNELL and ROBERT GORDON SINCLAIR, J. Biol. Chem. **118**:131, 1937.

Sinclair demonstrated several years ago that the brain is unusual in showing no definite changes in the composition of its phosphatides when the fat in the animal's diet is changed. This observation has now been investigated further by McConnell and Sinclair by means of feeding a readily identifiable fatty acid (elaidic acid), which under most circumstances enters phosphatide molecules with ease. They found that the phosphatides of the brains of rats that have been fed large amounts of this acid throughout the entire period of prenatal and postnatal development contain only about one-fourth the amount of elaidic acid found in phosphatides of the liver and muscles. It is their opinion that there is a greater degree of selection in the synthesis of phosphatides in the brain than in that of phosphatides in the liver and muscle.

PAGE, Indianapolis.

THE NUMBER OF NEUROHUMORS IN THE CONTROL OF FROG MELANOPHORES. GEORGE HOWARD PARKER and LOUISE E. SCATTERTY, J. Cell. & Comp. Physiol. **9**:297 (April) 1937.

The dark phase of the frog (Rana pipiens) is due to a dispersing neurohumor carried in the blood of the animal. The blanching of Rana pipiens is ascribed merely to the absence from the blood of the dispersing neurohumor, probably intermedin, by which the animal is darkened. Rana pipiens shows only very slight nervous control over its melanophores; the melanophore system is controlled mainly on a humoral basis. Some amphibians, like Xenopus, appear to be bihumoral. The plan of chromatophoral action is not the same in fishes, amphibians and reptiles.

CHORNYAK, Pittsburgh.

THE DEVELOPMENT OF HEARING IN THE OPOSSUM. EDWARD MCCRADY JR., ERNEST GLEN WEVER and CHARLES W. BRAY, J. Exper. Zoöl. **75**:503 (April) 1937.

The development of auditory function was studied in pouch young opossums by observing reflex motor responses to pure tones produced by a loud-speaker, and the electrical responses were recorded from the round window or the acoustic tracts during stimulation with sound. Both types of tests indicated an early appearance of sensitivity to tones of the middle range and progressive growth of

sensitivity to higher and lower tones. The complete range was attained at weaning, when the young left the pouch. The results support the view that tones of from 1,000 to 3,000 cycles are focalized in the distal portion of the basal coil and that the range is extended in both directions by differentiation of neighboring structures. The foci for all tones of from 3,000 to 25,000 cycles are crowded into the proximal portion of the basal turn of the cochlea, and the foci for lower tones are spread out toward the apex. The sensitivity of the opossum's ear is less than that of the guinea-pig's, especially for low tones. The lower limit for the opossum is about 100 cycles. Maximum sensitivity is at first near the middle of the range and with increasing age shifts upward about two octaves (to about 7,000 cycles). At all ages and at all frequencies of stimulation, there is a nearly linear relation of the electrical response to the intensity of the stimulus. This indicates a highly efficient electro-acoustic apparatus. WYMAN, Boston.

CORTICAL FACILITATION WITH ELECTRICAL STIMULI. E. D. ADRIAN, J. Physiol. **89**:1P, 1937.

With single stimuli or with a very short series weak enough to excite directly only elements in the superficial cortical layers, facilitation was induced in adjacent cortical areas in the cat, rabbit and monkey when the animal was under barbiturate anesthesia. McCOUCH, Philadelphia.

THE DEVELOPMENT OF THE "RIGHTING" MOVEMENTS IN THE FOETAL SHEEP. J. BARCROFT and D. H. BARRON, J. Physiol. **89**:19P, 1937.

Between the forty-seventh and the fiftieth day of intra-uterine life (the total gestation period being about one hundred and fifty days), the fetal sheep, when lying on a solid surface, attempts to raise its head and to stand (with the forelimbs extended and the hindlimbs flexed at the hip) in response to stimulation of the snout. This response is not obtainable at either earlier or later periods of fetal life.

McCOUCH, Philadelphia.

ACTION OF PROSTIGMIN ON SPINAL CORD IN MAN. M. KREMER, H. E. S. PEARSON and SAMSON WRIGHT, J. Physiol. **89**:21P, 1937.

Prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate) was administered by intrathecal injection to eight patients with a spastic condition, in doses of from 1 to 1.5 mg. It induced transient depression of spasticity and reflexes preceded by pallor, vomiting and drowsiness.

McCOUCH, Philadelphia.

THE FORMATION OF ACETYLCHOLINE BY BRAIN TISSUE. EDGAR STEDMAN and ELLEN STEADMAN, J. Physiol. **89**:37P, 1937.

Minced brain tissue is ground with a solution of physostigmin in chloroform and the mixture incubated at 37 C. for from one to four hours. Acetylcholine has been extracted from the mixture in crystalline form and identified chemically.

McCOUCH, Philadelphia.

PHYSIOLOGY OF GALVANONARCOSIS IN WATER ANIMALS. F. SCHEMINZKY, Arch. f. d. ges. Physiol. **237**:273, 1936.

A state of paralysis similar to narcosis (galvanonarcosis) was produced in crabs and fishes when a galvanic current was conducted through the animals in a descending direction (anode on head and cathode on tail); it disappeared immediately when the current was interrupted. The ascending current produced general muscular spasm, which fixed the animals in place (fixation). Galvanonarcosis could not be produced in echinoderms; the current induced spasm of the muscles

regardless of its direction. Galvanonarcosis as well as fixation is due to action on the central nervous system. The antagonistic effect of the descending (paralyzing) and the ascending (stimulating) current may be explained by the production of anelectrotonus and catelectrotonus, respectively, at the point of emergence of the neurite from the nerve cell. Further studies, however, are necessary to ascertain whether an arrangement of the nerve cells really exists as propounded by this theory.

SPIEGEL, Philadelphia.

NATURE OF GALVANONARCOSIS IN FROGS. F. SCHEMINZKY, O. HOCHSTÄDT and P. ADLER, Arch. f. d. ges. Physiol. **237**:284, 1936.

A descending current (anode on the head and cathode in the cloaca) induces relaxation of the skeletal muscles with absence of action currents. An ascending current induces spasms of the muscles, with violent action currents; after a while the spasms disappear, owing to central fatigue, but action currents are still present. During application of the descending current, the excitability of the spinal cord, tested by direct and reflex stimulation, is abolished; during application of the ascending current it is increased. This refutes the theory of Loeb that the ascending and the descending current have the same effect on the central nervous system. The decrease in excitability produced by the descending current is followed by an increase; conversely, the increase in excitability produced by the ascending current is followed by a decrease. These changes are similar to the electrotonic effects produced in peripheral nerves. This suggests that the various effects of the galvanic current on the central nervous system are due to electrotonic phenomena.

SPIEGEL, Philadelphia.

EXPERIMENTAL CHANGES IN PHYLOGENETIC RELATIONS OF SPINAL INNERVATION. P. ANOCHIN and A. IWANOW, Arch. f. d. ges. Physiol. **237**:558, 1936.

Nerve trunks with opposing functions were "crossed" in dogs. The obturator and femoral nerves were severed, and the central part of each nerve was united with the distal part of the other. For two months after operation the hindlegs were paralyzed on the side of operation. During the following month the animals were able to stand on their hindlegs, but locomotion of the forelegs was independent of that of the hindlegs, and the latter moved by jumping simultaneously with the forelegs. After about eight months normal coordination of all four legs was restored. Regenerating nerve fibers grew into the paralyzed muscles after two months. This result is not in agreement with the resonance theory of Weiss. After removal of the motor cortex the process of reintegration takes longer than in the presence of a normal cortex. Conditioned defense reactions in the legs on the side of operation could not be elicited one and a half years after regeneration.

SPIEGEL, Philadelphia.

DISTURBANCES IN THE ISOLATED CONDUCTION OF IMPULSES IN THE NERVE TRUNK INJURED BY HYPERTONIC SOLUTIONS OR BY DRYING. D. G. KWASSOW and A. J. NAUMENKO, Arch. f. d. ges. Physiol. **237**:576, 1936.

The effect of concentrated solutions of neutral salts and of drying on the sciatic nerve of frogs was studied. The isolated conduction of impulses in the nerve is disturbed, so that threshold stimulation of peripheral branches of the nerve may induce contractions in muscles that are supplied by other fibers. Such effects are best observed with a frequency of from 20 to 50 per second, while higher frequencies (from 100 to 200) induce phenomena of inhibition. The excitability of the fibers is also altered by hypertonic solutions; as a rule it is increased, but it may be preceded by a short phase of decreased excitability. The disturbance of isolated conduction appears only if the excitability of the fibers is markedly increased.

SPIEGEL, Philadelphia.

ANALYSIS OF THE PHYSICAL REGULATION OF RESPIRATION BY ACTION POTENTIALS OF THE PHRENIC NERVE. W. R. HESS and O. A. M. WYSS, Arch. f. d. ges. Physiol. **237**:761, 1936.

In order to study the activity of the respiratory center, the action potentials of the phrenic nerve in rabbits were recorded by a cathode ray oscillograph. Impulses were found in the phrenic nerve during apnea. Their intensity depends on the state of dilatation of the lung. They are maximal when the lung is collapsed and minimal or absent when the lung is inflated. Tonic impulses are present in the phrenic nerve during spontaneous respiration, since action currents do not completely disappear but are diminished during expiration. The frequency of spontaneous respiration is also influenced by the state of dilatation of the lung; it is higher the less the lung is inflated. If inflation or deflation of the lung is maintained for some time, adaptation to this new state is observed in that the effect produced by inflation or deflation diminishes, first at a faster and then at a slower rate. The experiments confirm the view that the vagus nerves have a tonic influence on the respiratory center.

SPIEGEL, Philadelphia.

BEHAVIOR OF THE CENTRAL NERVOUS SYSTEM (SPINAL CORD OF THE FROG) UNDER THE EFFECT OF HIGH PRESSURE. U. EBBECKE, Arch. f. d. ges. Physiol. **237**:785, 1936.

Spinal cord preparations of frogs were hung in a pressure bomb and observed through a window. Rhythmic clonic movements of the extremities appeared at pressures of from 50 to 100 atmospheres and reached a maximum at pressures of from 150 to 250 atmospheres. These movements show that the central nervous system responds to a continual, constant pressure by a rhythmic type of reaction. A pressure of 300 atmospheres, while innocuous for the nerves and muscles, paralyzes the central nervous system. This paralysis is first reversible and later irreversible. The central nervous system is particularly sensitive to compression.

SPIEGEL, Philadelphia.

Neuropathology

LESIONS OF THE NERVOUS SYSTEM OF THE RAT IN VITAMIN B DEFICIENCY. CHARLES DAVISON and LEO STONE, Arch. Path. **23**:207 (Feb.) 1937.

The clinical syndromes and especially the neuro-anatomic lesions induced by the administration of diets deficient in the vitamin B complex to animals (rats, cats and dogs) are apparently not constant. Most observers agree on the changes induced in the peripheral nerves of some animals as a result of deprivation of the antineuritic component (B_1). Not all, however, agree on the lesions produced in the spinal cord and higher neural centers. Furthermore, a number of observers are of the opinion that the nerve lesions are due not directly to the vitamin B deficiency in these artificial diets but entirely to the inevitable factor of inanition. Certain investigators compare the focal demyelinization induced in the spinal cords of dogs by vitamin B deprivation with the well defined neuropathologic picture of subacute combined degeneration of the spinal cord in man (pernicious anemia).

In the experiments undertaken by Davison and Stone, vacuolation, liquefaction necrosis and chromatolysis of ganglion cells in the mesencephalon, metencephalon and spinal cord, as well as disintegration of the myelin sheaths of the peripheral nerves, were observed alike in the animals subjected to diets totally and subtotally deficient in vitamin B_1 or in vitamins B_1 and B_2 and in those suffering from pure inanition. Neurologic symptoms, such as ataxia, dragging of the extremities, convulsions, priapism and tonic retractions of the head, occurred in the rats which died of nutritional deficiency. They were less marked in the animals subjected as controls to pure inanition than in the animals deprived of vitamin B_1 or of vitamins B_1 and B_2, probably because of the short duration of life of the first group.

The question of the relationship between the nervous symptoms of the rats and the histologic changes described could not be answered easily. The paresis or paralysis of the extremities could be ascribed to peripheral neuritis, and the convulsions and tonic retractions of the head, to hemorrhages and changes in the nerve cells in the mesencephalon and metencephalon. These observations were analogous to those described by Hofmeister, who fed rats a diet which was deficient only in vitamin B. The ataxia, asthenia and equilibratory disturbances could be the result of inanition and weakness. It is emphasized that the deprivation of vitamins expresses itself early in loss of appetite with consequent inanition.

The specific changes in the ganglion cells, of which vacuolation was the most prominent, were of the type encountered in nutritional diseases, high fever, extreme exhaustion, prolonged disease, drug intoxications and technical defects due to fixation. In view of the uniformity with which these changes occurred and of the special care in the fixation and staining of the tissues of these experimental animals, Davison and Stone consider that the changes represent a true pathologic state. The histologic changes, as well as the clinical phenomena, were less severe in the group with inanition than in the other groups, except in the peripheral nerves, where the changes were more marked. The administration of abundant vitamin B to the animals subjected to starvation did not prevent the occurrence of pathologic changes essentially similar to those occurring in the animals deprived of vitamin B_1 or of vitamins B_1 and B_2. This seemed to indicate that inanition is an important factor in the direct pathogenesis of the lesions associated with deficiency of vitamin B. The anorexia resulting in inanition is caused probably by the avitaminosis.

WINKELMAN, Philadelphia.

THE CONNECTIVE TISSUE REACTION IN MULTIPLE AND IN DIFFUSE SCLEROSIS. LESTER S. KING, Arch. Path. **23**:338 (March) 1937.

It has long been recognized that certain pathologic conditions affecting the central nervous system are accompanied by an overgrowth of reticulin, or argyrophilic connective tissue fibers. Thromboses and gummas especially, and to a lesser degree tuberculomas, as well as lacerations and mechanical injuries show rich argyrophilic networks of connective tissue. In dementia paralytica, Achúcarro was the first to describe delicate reticulin networks around the blood vessels in the cortex, an observation which has since been amply confirmed.

In the primary demyelinizing diseases the connective tissue reaction has received relatively little attention. The group of diffuse scleroses has been studied with the required specific technic in only a small proportion of cases. Of the cases so studied, these reticulin nets have been shown in some and not in others. The literature has been adequately reviewed in Bouman's recent monograph. In multiple sclerosis mesenchymal nets have occasionally been described, but until the recent work of Peters the subject has not been adequately investigated.

In each of thirteen cases of multiple sclerosis studied by King, networks of argyrophilic connective tissue fibers were observed growing diffusely into the parenchyma. The extent of this growth varied from case to case and even from plaque to plaque. In part the reticulin nets grew from blood vessels of small caliber, predominantly capillaries and precapillaries; in part they appeared to grow independently of preexisting reticulin. Diffuse invasion of reticulin may be one of the early pathologic reactions in multiple sclerosis and is observed not only in the white matter but in the cerebral cortex and other gray masses. The growths appear to be definitely related to the disintegration of myelin, with the intensity of the process playing some rôle. Such reticulin nets bear no correlation with the degree of gliosis, destruction of axis-cylinders or perivascular infiltration. This type of connective tissue proliferation takes place independently of fibroblasts.

Eleven cases of diffuse sclerosis studied can be divided into three groups, in the first of which no reticulin network was shown, in the second a slight or moderate growth similar to that in multiple sclerosis and in the third a profound growth, showing qualitative as well as quantitative differences from that of multiple sclerosis. King suggests that diffuse sclerosis does not represent a unitary condition.

WINKELMAN, Philadelphia.

ANATOMOCLINICAL STUDY OF A CASE OF CHOREA MOLLIS. G. MARINESCO, S. DRAGANESCO, S. AXENTE and I. BRUCKNER, Ann. de méd. **40**:397, 1936.

This rare disease, which has been described by West as limp chorea and by Gowers as chorea paralytica, does not present any definite pathologic changes in the central nervous system but is associated with degenerative changes of the striated muscles. The authors describe the case of a girl aged 15, who one year before admission had suffered from rheumatic arthritis. About one month before admission her movements became incoordinate; gradually choreiform movements appeared in both the face and the extremities. The tendon and cutaneous reflexes disappeared, but sensation was not affected. The choreiform movements disappeared gradually and were followed by flaccid paralysis of the extremities. Severe septicemia developed, and the patient died ten days after admission.

Autopsy revealed acute swelling of the spleen, fatty degeneration of the liver, glomerulonephritis, pericarditis and endocarditis, with severe lesions of the mitral valves and fatty degeneration of the cardiac muscle. The muscles of the extremities showed fatty degeneration, together with perivascular lymphocytic infiltration and complete disappearance of glycogen. In the spinal cord there was mild myelitis, with acute changes in the ganglion cells. The histopathologic lesions of the brain were vague: widespread chromatolysis of neurons and mild satellitosis within the basal ganglia, without marked disease of the neurons. Besides, there was mild distention of the meningeal veins, with scattered, minute perivascular hemorrhages and mild lymphocytic infiltration.

The authors discuss the relative significance of these pathologic changes in view of the clinical manifestations of choreiform movements. They emphasize the widespread pathologic alteration of the central nervous system without predilection for any single nucleus, a fact which does not support the idea of localization of the morbid process in the neostriatum. The transformation of active chorea into chorea paralytica in this case can be explained by the myositis and the degenerative changes in the striated muscle fibers, but not by a lesion of the central nervous system.

WEIL, Chicago.

ADDISON'S DISEASE AND SCLEROSING DISEASE OF THE WHITE MATTER OF THE BRAIN. E. HAMPEL, Deutsche Ztschr. f. Nervenh. **142**:186 (Jan.) 1937.

A man aged 23 showed progressive brownish discoloration of the skin and extreme exhaustion with low blood pressure. Death occurred eight years after onset of the first symptoms in a delirious state, of sudden onset and two days' duration. The patient had not given any evidence of neurologic disease during life, and neurologic examination even shortly before death revealed only a Babinski sign on the left. Autopsy revealed diffuse sclerosis of the white matter of the brain, which spared the U fibers. There was no fatty degeneration. Demyelinization was most striking around the ventricles. Furthermore, an abundant growth of macrophages and a new formation of mesenchymal fibrils were observed in different parts of the white matter of the brain and in the pons. Hampel points out the possibility of a connection in this case between the lesions of the brain and the atrophy of the adrenal glands.

ADLER, Boston.

HISTOLOGIC INVESTIGATIONS ON THE EFFECT OF ROENTGEN RAYS ON THE CENTRAL NERVOUS SYSTEM OF THE RABBIT. R. KOIDUMI, Psychiat. et neurol. jap. **41**:4 (Jan.) 1937.

Both embryo and adult rabbits were used in this investigation. From one to nine exposures of roentgen rays, in skin doses of from one-third to ten units, were applied to the head or other parts of the body. The results were as follows: 1. The effect of roentgen rays on the central nervous system is chiefly on the mesodermal structures, particularly the blood vessels, and leads to disturbance of the hemato-encephalic barrier and to impairment of permeability of the walls, so that serious infiltration or bleeding occurs, followed by necrosis or softening of

the tissue. 2. There is hyperplasia of the glia cells and blood vessels, followed by tissue organization as a result. 3. The microglia cells react actively in the initial stages, forming typical gitter cells in the areas of necrosis or softening. The astrocytes hypertrophy. 4. In adult rabbits the nerve cells remain almost unaffected, while in embryos and new-born rabbits they undergo severe changes. 5. With vital dyes the vascular endothelium and glia cells are seen to contain pigments.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

INSANITY IN PRIESTS AND RELIGIOUS. DOM THOMAS VERNER MOORE, Ecclesiastical Rev., November-December 1936, vol. 95.

The fact that Dom Moore is a priest belonging to a religious order, a member of the faculty of Catholic University and a well known psychologist and author, lends authority to this interesting survey. He has painstakingly investigated the various state, county and private hospitals, Catholic and non-Catholic, and enumerated the number of priests, nuns and brothers who were mentally ill. He then checked these findings against the numbers of priests, nuns and brothers in the United States, to determine the percentages. He also contrasted his findings with the general statistics on the numbers of single, married, widowed and divorced persons who become mentally ill. The number of religious devotees who suffer from mental disease is remarkably small in comparison.

Dementia praecox leads the list of illnesses, as it does in every day life. Apropos of this, Dr. Moore says: "There can be no doubt that a number of prepsychotic personalities are attracted by the cloistered life. Furthermore, the model child type of praecox behavior is very likely to be mistaken for piety."

The figures indicate that the strain of community life does not cause mental disease among nuns and suggest that all applicants for entrance to a cloistered religious life should be examined with a view toward eliminating those who are prepsychotic. To this end Moore formulates a series of questions and a character study to be used for all applicants. These investigate the family, the personal history of the candidate, and his inclinations and emotional traits, particularly his irritability. Moore discusses briefly several cases and in conclusion suggests that the questions he propounds, or similar ones, be put into small booklets. These booklets would be given to (*a*) the applicant, (*b*) a member of the family and (*c*) the parish priest or some one outside the family. In this way the incidence of mental illness in priests and nuns might be made even lower than it is now.

BRACELAND, Philadelphia.

THE ATTITUDE OF MURDERERS TOWARDS DEATH. PAUL SCHILDER, J. Abnorm. & Social Psychol. **31**:348 (Oct.-Dec.) 1936.

A questionnaire concerning attitudes toward death was submitted orally to thirty-one patients who were being examined pending trial for murder in the first or second degree. The study was intended not to solve the basic problem of murder but merely to elucidate a largely neglected point in criminology, namely, the attitude of the murderer toward death. The first group of nine patients showed no particular concern about death. With them, heterosexuality was a superficial pleasure. There was never a deep relation between death and erotism. All the subjects considered themselves kind hearted and good, and all professed a deep interest in their parents. Most of the murders in these cases had occurred in connection with hold-ups and brawls. Akin to this group were two cases in which the action came suddenly, without any particular motive and without any conscious desire to kill. In the next group of four cases preoccupation with the idea of death played a great part. In one half of these cases there were anxiety dreams of falling or being struck. In two cases a severe Ganser syndrome was elicited.

In group two the motives were more easily understandable, and a rational cause for hostility was discernible. In two of these cases it was determined that the subjects wished to punish their homosexual partners for having seduced them and also to punish themselves for having been seduced. The latter aspect in one case was so strong and so involved with feelings of guilt and self-recrimination that the suicidal urge was as strong as the homicidal. Group 3 comprised patients with severe psychopathy and psychosis. In the case of a very weak character death was regarded a state of peace; examination found deep dependence on his mother. In another case conscious motives of almost paranoid character were in the foreground. This leads to a group of murderers with outspoken psychosis, two or three of whom insisted on asserting that their murdered victims were yet alive. From the study of these cases Schilder draws the following conclusions: 1. Death may signify escape from an unbearable situation. One identifies death with a new life exempt from any of the difficulties of the present life. The idea of death thus becomes something to play with. There is a close relation between this psychologic attitude and what is known in animal psychology as the reflex of sham death. 2. Death may serve the end of forcing others to give more affection than they are otherwise willing to grant. 3. To be killed may be an equivalent for the culmination of sexual intercourse. 4. Death may mean the final narcissistic perfection which grants lasting and unchallenged importance to the individual self. 5. Death gratifies the masochistic tendencies, with the promise of perpetuated self-punishment (the opposite of conclusion 1). The eternity of hell-fire reflects this psychologic attitude.

WISE, Howard, R. I.

MEDICINE, THE LAW, AND JUVENILE DELINQUENCY. SMITH ELY JELLIFFE, J. Crim. Law & Criminol. **27**:503 (Nov.-Dec.) 1936.

Psychiatry is no longer a narrow study of the psychotic person. The psychiatrist is an observer of the conduct of the entire organism. There is a shift in the legal point of view from the punitive to the prophylactic. Science per se is interested in the relation of the organism to its environment, i. e., ecology, so that psychiatry is now taking more and more this point of view. The change dates to freudian psychology, which deals with understanding of the depths of personality. Delinquency represents something which can be found in all persons; social agencies modify this factor. With the development of the psychiatric point of view, agencies may be able to play an important part in the treatment of delinquency. The psychiatrist offers help to the law in determining the influence of the milieu in the formation of the superego. One can illustrate this by pointing to the Whittier Correctional School, near Los Angeles, where this point of view has been invoked.

SELLING, Detroit.

HEARING DEFECTS IN BEHAVIOR PROBLEMS. MATTHEW MOLITCH and EDGAR M. ADAMS, J. Juvenile Research **20**:15 (Jan.) 1936.

Studies were made with audiometers on 480 inmates of a home for boys. Defective hearing was associated with a lower intelligence level in this group than in the rest of the population. A high incidence of hearing defects was found in children with otitis media and syphilis. Those with reading defects rated third and were followed by children with the so-called psychopathic personality, endocrine disturbances and problems of discipline.

FERGUSON, Niagara Falls, N. Y.

NASOPHARYNGEAL SEPSIS IN 2,056 CASES OF MENTAL DISORDER. T. C. GRAVES, Brit. M. J. **1**:483 (March 6) 1937.

This paper summarizes briefly 2,056 cases of infection of the nose and throat occurring in the patients of the Birmingham Mental Hospital during a period of eight years. The sexes were about equally represented. Adenoids were removed in 129 instances, and tonsils, in 1,186. Diseased nasal sinuses were found in 1,425

patients. Graves says that mental symptoms may be among the first manifestations of "closed nasal sinus infection." The inference to be drawn is that certain psychoses may be improved or cured if infected sinuses are recognized and treated.

ECHOLS, New Orleans.

EFFECT OF ACETYL CHOLINE ON SOMATIC SYMPTOMS OF ANXIETY. M. S. JONES, J. Ment. Sc. **82**:785 (Nov.) 1936.

Jones chose for treatment six patients with anxiety neurosis, each of whom showed somatic manifestations of anxiety, such as tachycardia, palpitation, tremor, sweating, vasomotor instability, giddiness, weakness and a feeling of constriction in the throat or chest. Fourteen subcutaneous injections of 0.00025 Gm. of carbaminoylcholine chloride were given daily. This drug has an action similar to that of acetylcholine and is a stimulant of the parasympathetic nervous system. The results obtained from subjective and objective observation in these cases were in accord with the original conception that the symptomatology could be understood almost entirely in terms of autonomic imbalance, and in the cases in which it was possible to reproduce with epinephrine the somatic symptoms of anxiety the psychic manifestations of fear were reproduced at the same time. That in an attack of acute anxiety the symptoms are almost wholly referable to the sympathetic nervous system is evident from the symptoms complained of by these patients during an attack, and the cessation of symptoms following stimulation of the parasympathetic nervous system is in support of this. There would appear to be some justification for this treatment in cases in which attacks of acute anxiety are shown, provided this is in no way meant as a substitute for psychotherapy and aims merely at giving the patient more rapid relief from the distressing symptoms accompanying anxiety than could be attained by purely psychologic methods. Relief from the psychic and somatic symptoms of anxiety resulted in all cases, but they tended to relapse after withdrawal of the drug. EDITOR'S ABSTRACT. [J. A. M. A.]

INTERMITTENT PSYCHIC MIOPRAGIA. PAUL COURBON and J. CHAPOULAUD, Ann. méd.-psychol. **95**:76 (Jan.) 1937.

The authors report the case of a man aged 21, whose mental age was 9 years and who, since early childhood, had been subject to periodic crises characterized by profound changes of personality, with impairment of psychic validity, loss of elementary ethical sense, cynicism, intemperance and immorality, often associated with hypersomnia. This paroxysmal psychic "miopragia" occurred every five or seven weeks and lasted for several days. It disappeared as abruptly as it appeared. Afterward, the subject was his normal self. There were no symptoms pointing to epilepsy, narcolepsy, cataplexy or familial periodic paralysis. The crises of psychic miopragia occurred without apparent external physical or emotional causes. All the crises which occurred while the patient was in the community were associated with agitation and impulsive behavior, which, the authors believe, was provoked by the reprobative attitude of persons in the patient's environment.

YAKOVLEV, Waltham, Mass.

DIPSOMANIA IN WOMEN. G. PISK, Monatschr. f. Psychiat. u. Neurol. **93**: 218 (June) 1936.

Although German investigators have stated that dipsomania is rarely observed in women, certain French authors have claimed that it is commoner in women than in men. From a study of the figures from a clinic in Vienna, Pisk found that a diagnosis of dipsomania was made in 1.9 per cent of all female and 1.7 per cent of all male alcoholic patients. However, a scrutiny of the symptoms noted in eight female patients showed that only three presented features typical of dipsomania. In five patients chronic alcoholism and a decreased tolerance to alcohol were associated with a tendency to increased drinking during menstruation, as a result of which a clinical picture resembling that of dipsomania was

produced. In the three typical cases there was great tolerance to alcohol, and the patients had distinct attacks in which feelings of unrest or anxiety ushered in an irresistible desire to drink large quantities of alcoholic beverages. The attacks usually occurred during menstruation and were often accompanied by an increase of libido. At the end, depressive moods with self-accusatory tendencies were observed. One patient had neurosyphilis and showed signs of involvement of the ocular muscles; another had had epidemic encephalitis, after which adiposity and a change of character had developed. These observations suggest strongly that the occurrence of dipsomania in women is at least determined partly by organic involvement of the brain, with disturbances in the region of the interbrain and midbrain probably playing an important rôle.

ROTHSCHILD, Foxborough, Mass.

ENGRAFTED SCHIZOPHRENIA AND EARLY DEMENTIA OF SCHIZOPHRENIC ORIGIN. A. GLAUS, Schweiz. Arch. f. Neurol. u. Psychiat. **37**:238, 1936; **38**:37, 1936.

Although the term "engrafted schizophrenia" (*Pfropfschizophrenie*) implies merely a combination of schizophrenia and mental deficiency, it has given rise to much confusion, since some authors classify as examples of *Pfropfschizophrenie* cases usually excluded from this group. In an attempt to clarify the situation, Glaus describes eleven cases in detail. The first two cases are included merely to show the need of care in diagnosis, since even psychiatrists of wide experience may falsely assume mental deficiency to exist in cases in which further observation will establish the diagnosis of uncomplicated schizophrenia.

The five patients in the second group were either imbeciles or morons, previously well adjusted socially for the most part, in whom in the fourth or fifth decade of life there developed a psychosis with hebephrenic, catatonic or paranoid features. In cases in which there was a gradual onset, the psychosis was preceded by changes in character, anomalies of mood and a tendency to catathymic ideas. The course in general was progressive, with emotional deterioration, even in cases in which the onset was acute. Except that the delusions were poorly elaborated and showed considerable poverty of content, the so-called oligophrenic pathoplastic state was lacking. The patients were all inaccessible.

In contrast to the patients in the aforementioned group, four patients in the third group had shown anomalies of character even in childhood and were given to reactions of a type suggesting hebephrenia. Psychotic symptoms appeared much earlier in these patients, but emotional rapport was retained to a considerable degree; remissions were frequent, and there was much less deterioration, in spite of definite changes in personality. Catatonic and paranoid symptoms were generally lacking, and psychogenic reactions were observed even at the height of the psychosis. Although these cases could hardly be regarded as examples of infantile dementia praecox, the schizophrenic trend was, nevertheless, evident early in life. In contradistinction to Kraepelin, who proposed the term *Pfropfhebephrenie* for conditions of this type, Glaus prefers the term "schizophrenic early dementia."

DANIELS, Denver.

CONTRIBUTION TO KNOWLEDGE OF RELATION BETWEEN RICKETS AND MENTAL DEFICIENCY. T. BRANDER, Finska läk.-sällsk. handl. **79**:957 (Nov.) 1936.

From somatic and psychologic examination of 375 children of premature birth, ranging in age from 7 to 15 years, Brander found that in the group with grave traces of early rickets there was greater frequency of feeblemindedness and states bordering on feeblemindedness and ordinary stupidity, while the number of normal and talented children was correspondingly less. Since the defects in intelligence were of relatively mild degree, he concludes that rickets can hardly be of practical significance in the etiology of oligophrenia. There was no evidence for or against rickets as leading to lasting mental deficiency of mild degree, but both rickets and defective mental development might have the same cause, as, for example, premature birth. It seems fairly certain to the author that mental deficiency in itself promotes the origin of rickets. EDITOR'S ABSTRACT. [J. A. M. A.]

STUTTERING: NEUROPSYCHIATRIC ASPECT OF THE STUTTER PHENOMENON. F. GREWEL, Psychiat. en neurol. bl. **41**:16 (Jan.-Feb.) 1937.

The stuttering mechanism is analyzed from the point of view of the constitutional, coordinative and neurotic factors. From a review of the literature Grewel concludes that a constitutional tendency to stuttering can be traced in some cases, although it seems not to play a decisive rôle. Coordination of speech apparently is of greater importance. Some of the phenomena well known in organic nervous diseases, such as perseveration, reiteration, logoclonia, echolalia and palilalia, show a marked resemblance to stuttering. Considerable difficulty in any analysis arises from incomplete definition of the word "stuttering" as well as of many of the aforementioned organic speech defects. The closest organic parallelism to the phenomenon of stuttering is seen in palilalia. The stuttering factor in palilalia is considered to be cortical. The striatal localization of stuttering is rejected. One of the factors involved in the development of stuttering, especially between the fourth and the sixth year of age, is found in insufficient automatization of speech. The motor component of stuttering is assumed to be analogous to that of subcortical motor aphasia.

These considerations point to the presence of a psychic mechanism. One may think in this connection of the babble of children or of the iteration of primitive languages. Following this trend of thought, stuttering may be conceived of as an emotionally conditioned regression to a primitive speech mechanism. Stocker pointed out that stuttering is analogous to ideomotor parapraxia. On the other hand, the stutterer, besides his leading symptom shows a number of signs which are common in neurotic persons, such as torsion movements of the head, fixation of one point, flushing, blowing out the cheeks, rubbing the hands and folie de doute, uncertainty, timidity and lack of self-confidence. The significance of the neurotic phenomena of stuttering is seen in the wish not to pronounce certain letters. Here the mechanism which forms the basis for the incoordination of speech interferes.

Since stuttering is not a nosologic unit, treatment must be individualized. The importance of general psychic therapy is emphasized. Change of milieu, instruction of parents and building of character are of greater importance than exercise. The personality of the teacher is important. In the presence of deeper conflicts a psychiatrist is necessary.

LEWY, Philadelphia.

ATYPICAL PSYCHOSES IN ALCOHOL ADDICTS. S. HERINGA, Psychiat. en neurol. bl. **41**:47 (Jan.-Feb.) 1937.

The cases of two patients with atypical alcoholic psychoses are compared to illustrate the importance of the premorbid constitutional element in manifestation of the psychosis. The first patient, of a pyknic type, who was a chronic drunkard, had a subacute psychosis characterized by numerous optic, acoustic, sensory and olfactory hallucinations. In addition, there was a manic syndrome with expansive euphoria, fugitive ideas and confusion. In the course of one and one-half years a permanent state of slight dementia developed, accompanied by changes in character typical of chronic alcoholism. Heringa finds in this picture the combination of a pathogenic and a pathoplastic factor. He considers alcohol as the pathogenic factor and the structural peculiarities of the patient, which became manifest under the influence of alcohol, as the pathoplastic factor.

The second patient was a psychopathic person of the leptosomatic, asthenic type. He was a chronic drinker, had passed through a delirium once and had used bromural to excess in recent months. During the period of abstinence an acute psychosis appeared, characterized by a delirious state, hallucinations and complete incoherence. Gradually chronic confusion developed. Complete restitution followed in two years. In this person the manic component was less prominent. In the clownlike, bizarre behavior and the tendency to violence a quality of character was seen which had been discernible in the premorbid personality.

The fact that the same causative agent, alcohol, produced such different psychoses in two constitutionally different persons is a proof of Kraepelin's dictum that in every man his personal psychosis develops.

LEWY, Philadelphia.

Meninges and Blood Vessels

MENINGITIS COMPLICATING MUMPS AND ENCEPHALITIS COMPLICATING MEASLES IN THE SAME CHILD. M. L. BRIDGEMAN, Am. J. Dis. Child. **53**:804 (March) 1937.

A boy aged 6 had mumps, during which meningitis developed. The patient recovered at the end of nine days. The cerebrospinal fluid showed 119 cells per cubic millimeter, and negative Kolmer and Kahn reactions at the time of the meningitis. About three months later the child acquired measles, during which he became feverish, irrational and delirious. The spinal fluid was normal. He became rational in a few days.

WAGGONER, Ann Arbor, Mich.

OCULAR SIGNS OF THROMBOSIS OF THE INTRACRANIAL VENOUS SINUSES. FRANK B. WALSH, Arch. Ophth. **17**:46 (Jan.) 1937.

The ocular signs of thrombosis of the cavernous and lateral sinuses are well known, but there is no complete agreement regarding the mechanism producing them. The ocular changes of thrombosis of the superior longitudinal sinus are even less well understood. Some of the conditions hitherto diagnosed as serous meningitis, pseudotumor of the brain or chronic arachnoiditis may be due to thrombosis of the venous sinuses in the presence of an abnormal pattern of the sinuses. Walsh correlates some of these possibilities with the anatomicopathologic changes in septic thrombophlebitis of the cavernous and lateral sinuses.

Aseptic thrombosis occurs in the nonpaired sinuses, is rarely associated with purulent infection, shows a tendency to organization or resorption, is rarely complicated by meningitis and in one-half the cases is followed by extravasation into the brain and a tendency to softening. Septic thrombosis is characterized by occurrence in the paired sinuses, frequency of purulent infection, meningitis and cerebral abscess, a tendency to purulent degeneration of the thrombus and, rarely, occurrence of extravasations into the cerebrum and cerebellum.

The thrombi grow in the direction of the flow of the blood stream, but they may also develop in the opposite direction. Such retrograde development is frequent in the intracranial venous sinuses, where it may be accounted for by the absence of valves in many of the venous channels, as well as by the plentiful collateral circulation. Septic thrombi result in bacteremia and septicemia and, through direct extension, may give rise to abscess of the brain and meningitis.

In septic thrombophlebitis of the cavernous and lateral sinuses, chemosis appears to parallel the amount of exophthalmos, which may be unilateral or bilateral. The degree is variable and is much less marked when the cavernous sinus is involved through retrograde extension from the lateral sinus than when it originates from an anterior infection.

Edema of the lids is a striking feature in cases of fulminating thrombosis, especially when the thrombosis arises from an anterior infection. Infection, rather than vascular obstruction, accounts for swelling of the lids. Walsh agrees with Faulkner that swelling of the lower lid is not pathognomonic of thrombosis of the cavernous sinus and that it may be due to infection of the antrum or of the ethmoid sinus.

Paralysis of the extra-ocular muscles is an early symptom. Ptosis develops later. Behr expressed the belief that the external ophthalmoplegia is purely mechanical and is due to a lesion of the nerves in the cavernous sinus, caused by pressure or inflammation.

Internal ophthalmoplegia is rarely encountered at the first examination and is described as a late symptom. Parsons stated that paralysis of the external rectus muscle is the first sign of involvement of the second eye. He stated that such a paralysis is to be explained either by basilar meningitis or by increased intracranial pressure.

Anesthesia of the cornea occurs early, though increased corneal sensitivity has been observed. Cloudiness and necrosis of the cornea result from exposure. These

are of slight importance in establishing the diagnosis. The fundus may remain normal throughout the course of the disease. Generalized retinal edema may be apparent. Pulsation of the retinal arteries was observed in one case, but hemorrhages were infrequent.

Thrombosis of the longitudinal sinus usually commences in the middle fifth of the sinus. Anatomically, the high position of the sinus, the low pressure, the slow current and the presence of pacchionian bodies predispose to thrombosis. It occurs usually in cases of debility in infants and as a result of changes in the blood itself, notably in chlorosis. Jacksonian convulsions occur frequently. Symptoms of involvement of the pyramidal tract confined to the lower limbs may be present. Conjugate deviation of the eyes occurs often. Exophthalmos has been reported, but rarely. Papilledema and engorgement of the vessels of the scalp, retina and conjunctiva occur, but, on the other hand, there may be complete absence of these signs.

When the thrombotic process is septic and has extended to the longitudinal sinus from the lateral sinus, the prognosis for life is bad. Doyle, in describing this type, concluded: 1. In the absence of meningitis, early apathy or stupor in a patient with evidence of thrombosis of the transverse sinus indicates infectious thrombosis of the superior longitudinal sinus by retrograde extension, especially if associated with choked disks or convulsions. 2. When tumor or inflammatory disease can be excluded, jacksonian seizures showing progression from one foot to the other, or beginning in the foot and gradually involving the homolateral upper extremity, suggest impairment of the circulation of the cerebral veins and probably thrombosis of the superior longitudinal sinus. 3. Abrupt onset of symptoms of increased intracranial pressure with fluctuations suggests thrombosis of the superior longitudinal sinus, as well as ventricular tumor. Absence of progression after a fair length of time or actual regression of symptoms is suggestive of thrombosis of the superior longitudinal sinus.

Bilateral papilledema is the outstanding symptom of thrombosis of the lateral sinus. It may be unilateral at times.

SPAETH, Philadelphia.

LYMPHATIC CHORIOMENINGITIS. DEWITT DOMINICK, J. A. M. A. **109**:247 (July 24) 1937.

The three cases that Dominick reports illustrate the difficulties encountered in making a correct diagnosis of lymphocytic choriomeningitis. The usual clinical and laboratory procedures are inadequate. In case 1 the disease was thought to be typhoid or tuberculous meningitis until the clinical course and the positive results of a neutralization test for lymphocytic choriomeningitis definitely ruled out these conditions. In case 2 the diagnosis was first believed to be meningococcic meningitis. It was thought that on the tenth day of the disease a few acid-fast bacilli were observed in the spinal fluid. No more of these bacilli were seen. Tuberculous meningitis was seriously considered until the clinical course and the positive results of the neutralization test for lymphocytic choriomeningitis proved this diagnosis to be wrong. In case 3 the confusion caused by the observation of gram-positive diplococci was evident. The meningitis was later found not to be of the purulent type. The patient's serum did not contain neutralizing antibodies for the virus of lymphocytic choriomeningitis. It is possible that the meningitis arose secondarily to infection in the ethmoid sinuses. The exact cause of the pleocytosis will probably remain in doubt. In the three cases were fulfiled most of the postulates which Wallgren set down in 1925 in his description of the disease believed to be aseptic meningitis. These cases also simulated, particularly in the headache, constipation and course, the two cases reported by Scott and Rivers. The spinal fluid of all the patients showed persistent and nearly complete lymphocytosis. Clinically, the disease is more benign than either tuberculous meningitis or encephalitis. The course is generally short, and recovery occurs in nearly 100 per cent of cases. The neurologic changes when present are rarely localizing. The infectiousness of the disease is still debatable. Reports of observations on the cerebrospinal fluid

in cases of lymphocytic choriomeningitis indicate that the sugar content is between 40 and 70 mg. and the chlorides about 700 mg. or less per hundred cubic centimeters. Predominant lymphocytosis is always present. The protein content in cases of the severe form usually has a tendency to rise. To make and prove the correct diagnosis of this disease, the virus should be isolated from the spinal fluid. It apparently disappears soon after the tenth day. According to Rivers and Scott, neutralizing antibodies cannot be seen in the serum until after the sixth week from the onset of the disease. Because of the possible confusion with other forms of meningitis, it seems of great importance that if the virus is not obtained from the spinal fluid, the serum should be tested for neutralizing antibodies. It is possible for lymphocytic choriomeningitis to be confused with meningitis caused by other agents.

EDITOR'S ABSTRACT.

TUBERCLE BACILLI IN THE CEREBRO-SPINAL FLUID: RECOVERY. JOHN P. MCGUINNESS, Brit. M. J. **1**:169 (Jan. 23) 1937.

In a woman aged 31 there developed an acute confusional psychosis after a brief period of restlessness and depression. Two weeks later lumbar puncture was performed for the relief of persistent pyrexia, headache and irritability. The spinal fluid contained pus cells, lymphocytes and tubercle bacilli. A culture of the fluid remained sterile. Organisms were not observed on subsequent examinations of the spinal fluid. The patient's symptoms gradually subsided, and after six months she appeared to be well. She had not yet been discharged from the hospital at the time the report was written.

ECHOLS, New Orleans.

HAEMOLYTIC STREPTOCOCCAL MENINGITIS TREATED WITH PRONTOSIL: RECOVERY. C. F. LUCAS, Brit. M. J. **1**:557 (March 13) 1937.

Acute meningitis developed in a boy aged 9 years who had a discharging ear. Beta hemolytic streptococci were grown in pure culture from the spinal fluid. Two tablets of a derivative of sulfanilamide known as prontosil (hydrochloride of 4-sulfamido-2', 4'-diamino-azobenzene) were given by mouth three times a day, and 10 cc. of the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonic acid was injected intramuscularly each day. The patient's temperature became normal at the end of thirty-six hours. The drug was administered for eight days. Recovery was complete.

ECHOLS, New Orleans.

THE CEREBRAL CIRCULATION: SOME NEW POINTS IN ITS ANATOMY, PHYSIOLOGY AND PATHOLOGY. T. J. PUTNAM, J. Neurol. & Psychopath. **17**:193 (Jan.) 1937.

Putnam presents a survey of recent investigations of the anatomy, physiology and pathology of the cerebral circulation. Anatomically, it has been demonstrated that the cerebral arteries are not end-arteries but possess a rich system of anastomoses. Different regions in the brain show differences in vascular pattern, and these local peculiarities may account for the selective localization of diseases of the central nervous system. The cerebral vessels are under vasomotor control by the sympathetic system and react particularly to chemical stimuli. Thus, carbon dioxide, ether, histamine and amyl nitrite cause marked dilatation, whereas epinephrine and hypertonic solutions cause contraction of the cerebral vessels. This active mechanism is, however, accessory to the more important passive changes in the cerebral blood flow caused by variations in the systemic blood pressure. Putnam concedes the possibility that spasm of the cerebral vessels may cause clinical syndromes but doubts the rôle of vasospasm in epilepsy, migraine and the transient focal symptoms of arteriosclerosis.

Pathologically, even minor disturbances of the cerebral circulation may lead to permanent parenchymal damage. Acute general anemia, if complete and con-

tinued for about ten minutes, leads to permanent damage of the cortex. Mild chronic asphyxia, on the other hand, affects the myelin by preference and leads to conditions similar to diffuse sclerosis. The focal lesions produced by carbon monoxide and methyl alcohol poisoning are more likely the result of local thrombosis than of general asphyxia. According to Putnam, cerebral hemorrhage is regularly preceded by thrombosis, which may account for the rupture of the blood vessels. In circumscribed vascular closure there are transitions between changes which are not permanent and focal softenings. Diffuse, incomplete lesions are frequently the result of local venous thrombosis, affecting by preference the white matter, with resulting loss of myelin. Such lesions simulate closely those of perivenous encephalomyelitis. In the later stages the changes imitate those observed in multiple and diffuse sclerosis. Putnam is of the opinion that these various diseases are produced by disseminated thromboses of the small cerebral vessels resulting from chemical changes in the blood plasma and not by specific infectious agents. Partial anoxemia of the cortex leads to widespread focal or diffuse damage of the parenchyma, without the production of softenings, and this can be produced experimentally by obstruction of the capillaries from the venous side. The resulting histologic picture is similar to the cortical atrophy of dementia paralytica. Merritt and Putnam demonstrated that the latter may be due to obstruction of capillaries due to syphilitic endarteritis. The author concludes that there are few pathologic processes in the central nervous system which are not directly or indirectly the result of circulatory disturbance.

N. MALAMUD, Ann Arbor, Mich.

ARACHNOIDITIS OF THE BASE OF THE BRAIN. Rev. d'oto-neuro-opht. **14**:691 (Dec.) 1936.

De Morsier, basing his remarks on the study of twelve cases in which the diagnosis was confirmed at operation, called attention to the frequent association of arachnoiditis of the posterior fossa and chronic cholecystitis; this occurred in five cases in his series. A differential diagnosis of arachnoiditis of the posterior fossa and tumor of the cerebellum is often impossible. As regards the difference between arachnoiditis and hysteria, he recalled that only a short time ago arachnoiditis was classified as hysteria in many cases. Another striking fact is the relief from arachnoiditis with a variety of surgical procedures. No explanation of this is offered.

Jentzer expressed the opinion that it is more enlightening to compare the results of anatomicopathologic investigation with the clinical picture. He suggested that since the arachnoid has neither blood nor lymph vessels, it alone cannot be the point of departure of inflammation and that arachnoidosis is a more appropriate term. The variability of the symptoms is pathognomonic of leptomeningitis or pachymeningitis. During surgical intervention, sensitiveness of the meninges, collection of cerebrospinal fluid between the dura and the soft meninges, edema of the soft meninges and flattening of the convolutions are often observed. Microscopic examination of tissue, stained by Nissl's method, reveals neuroglia cells arranged in columns, atrophied and shrunken pyramidal cells and, with lipofuchsin, phagocytic cells. Postoperative results depend on the form of the disease present: In the serous type operation yields unexpectedly favorable results, and in the fibrous form the outlook is somber, in spite of surgical intervention.

Sargnon raised the question whether arachnoid cyst is infrequent in association with optochiasmatic arachnoiditis.

Coppez emphasized the importance to oculists of studies of arachnoiditis by neurosurgeons, especially in the help offered to patients with atrophy of the optic nerve. When optic atrophy is due to pressure the central fibers are usually the first to show degeneration, while in the atrophy due to arachnoiditis the peripheral fibers are first affected.

Dor did not share the opinion that "the various specialists do not see the same types of patients." They see the same types but do not use the same language to

interpret what they see. Henceforth, ophthalmologists must seek to distinguish which patients with papillary stasis, neuritis and atrophy of the optic nerve they themselves will treat and which they will refer to the surgeon.

Renard discussed the advantages in cases of arachnoiditis of early operation to prevent damage to vision. In most cases in which there is papillary stasis, visual acuity is not affected. In others, the stasis subsides after the operation, but normal visual acuity does not return. Intervention should be as early as possible, and the prognosis as to vision should be guarded.

DENNIS, San Diego, Calif.

Diseases of the Brain

CONVULSIVE SEIZURES IN ADULT LIFE. A. EARL WALKER, Arch. Int. Med. **58**:250 (Aug.) 1936.

In a review of 100 cases of convulsive seizures in persons over the age of 20, Walker finds that in 14 patients cerebral arteriosclerosis or hypertension was the etiologic factor, in 15 cerebrospinal syphilis, in 16 tumor of the brain and in 4 trauma; in 51 the responsible factor was unknown, and the condition, though beginning in adult life, was classed as "idiopathic epilepsy." In the 4 cases of posttraumatic origin there appeared to be a direct relationship between the convulsions and the injury. The interval between the accident and the first paroxysm varied from three days to eighteen months. In 1 of these cases, roentgenograms disclosed a foreign body embedded in the brain substance; in the other 3, abnormalities were noted by encephalography. Of the group of patients classed as "idiopathic" all had the first seizures before the age of 49, while 25 per cent of those in the remaining groups experienced the first attack after the age of 50.

Walker recommends encephalography for every adult whose seizures cannot be explained. In a large number of cases this procedure reveals distortions of the ventricles, abnormalities in the subarachnoid space, cerebral scarring, tumors and other organic abnormalities. If ventricular filling does not occur during encephalography, ventriculography should be performed. DAVIDSON, Newark, N. J.

PSEUDOCEREBELLAR ABSCESS. S. L. SHAPIRO, Arch. Otolaryng. **25**:17 (Jan.) 1937.

Infection of the brain may follow unnecessary trauma in premature probing for an abscess of the brain. Shapiro reports the case of a man with a discharging right ear. He had spontaneous nystagmus to the left. The signs of a fistula in the right ear, together with a live labyrinth and spontaneous nystagmus to the left, led to a diagnosis of chronic suppurative otitis media with circumscribed labyrinth on the right. In two weeks complete loss of hearing had developed on the right side, with spontaneous nystagmus to the left and past pointing to the right. There was leukocytosis. The spinal fluid pressure was normal, and the cell count was 4 per cubic millimeter of fluid. A diagnosis of diffuse suppurative labyrinthitis was made. The temperature began to rise; in three weeks mastoidectomy revealed erosion of the external horizontal canal by a cholesteatoma. A septic course followed the operation, and the jugular vein was ligated on the fourth postoperative day. Blurring of the disks, frontal headache, vomiting, choking of the disk of 3 diopters and increased spinal fluid pressure led to the diagnosis of abscess. Weakness of the right arm strengthened the suspicion of a right cerebellar abscess, but with watchful waiting the symptoms gradually subsided. The patient recovered and has been well for two years. Shapiro points out that this case may have been one of a right cerebellar abscess and gives the history in a second case occurring in the practice of a colleague in which a patient with somewhat similar signs recovered, only to die at a later period of an intercurrent disease. Autopsy revealed a healed cerebellar abscess. HUNTER, Philadelphia.

A Clinical Syndrome Indicating Cessation of Surgical Drainage from an Abscess of the Brain. J. M. Nielsen and Cyril B. Courville, Bull. Los Angeles Neurol. Soc. **2**:11 (March) 1937.

Nielsen and Courville state that as soon as an abscess of the brain is properly drained there should be relief from headache, increase in temperature and pulse rate, improvement in the mental state, cessation of vomiting and acceptance of food and water. They attribute the rise in temperature to disturbance of the inflammatory reaction in the walls of the abscess and the increase in the pulse rate to diminution in intracranial pressure and release of bacterial toxins. If drainage is inadequate, a train of symptoms results, which Nielsen and Courville divide into three stages: First, the patient has headache, irritability and restlessness and sleeps poorly—symptoms which probably result from an inflammatory reaction about the abscess. In the second stage pressure signs, such as anorexia, nausea, vomiting, drowsiness, incontinence, stupor and often convulsions, appear. During this period the temperature and pulse rate fall to a subnormal level. If no relief is given by proper drainage, the third stage supervenes, in which the patient lapses into coma and dies of respiratory failure, rupture of the abscess or meningitis. The authors identify these three periods with the three stages in the development of an abscess of the brain as described by Macewen. Appearance of such symptoms after drainage of an abscess indicates either that the drainage has become obstructed or that there is another abscess.

Mackay, Chicago.

Pituitary as Probable Factor in Origin of Headaches of Menopause. P. J. Reel and T. F. Lewis, Ohio State M. J. **33**:156 (Feb.) 1937.

On the assumption that the anterior lobe of the hypophysis undergoes abnormal physiologic hyperplasia after castration and during the menopause, Reel and Lewis believe that the explanation of the headache so often complained of lies in the fact that the pituitary gland is almost completely surrounded by bone. It lies, so to speak, in a box within a box, thus preventing any marked expansion from taking place except by greatly increasing the tension within the sella. This in all probability produces headache in the same manner as that induced by increased intracranial pressure. Pituitary headaches may be entirely occipital or suboccipital in type. Some patients complain of occipital pain transmitted bilaterally to the frontal or temporal areas. Quite commonly one entire side of the head is involved. Dull, heavy distress located behind the inner angles of the eyes is frequently encountered. The pain, regardless of type, is usually severe. It may be lancinating or may develop as a deep seated, heavy, dull ache. In fourteen of the nineteen patients whose chief symptom of the menopause was that of very severe headache, an abnormal amount of gonadotropic substance was demonstrated in the blood prior to irradiation, according to the Fluhmann technic. The roentgen treatments were given with 200 kilovolts at a distance of 50 cm. with 0.65 mm. of copper and 1 mm. of aluminum as a filter and an 8 cm. mask. A total of 1,000 roentgen units was used, divided into two exposures of 500 roentgen units each, administered a week apart and on opposite sides of the head. Other than temporary alopecia in two patients and slight transient parotitis in one, no complications or ill effects were encountered. After irradiation, fourteen of the nineteen patients showed a marked degree of improvement. Three of the remaining five were improved to some extent, while the remaining two received no benefit. The authors believe that the total dose has an inhibitory effect on the activity of the hypophysis. If this is true, it would seem safe to assume that the result was a diminution in the size of the gland and subsequent lessening of tension within the sella. Since the chief complaint of headache tends to disappear under this management without the aid of other forms of therapy, the conclusion may be justified that the pituitary is a highly probable factor in the causation of certain types of headache peculiar to the menopause.

Editor's Abstract.

Ocular Paralyses Following Mumps. T. Harrison Butler and A. J. Wilson, Brit. M. J. **1**:752 (April 10) 1937.

Two cases of mumps with neurologic complications are reported. The first is that of a boy aged 9, who had complete paralysis of the intrinsic muscles of the eyes. On examination five years later, the eyes were normal. The other patient, aged 12, had permanent, complete paralysis of the oculomotor nerve on one side several weeks after the parotitis.

Butler and Wilson point out that lymphocytic pleocytosis is present in most cases of mumps. Also, since meningitis and encephalitis sometimes precede the parotitis, they think that the virus should be considered as potentially neurotropic. They believe also that the peripheral neuritis which occurs in mumps is not toxic but is true meningoradiculitis. Cranial nerve palsies due to the virus of mumps may occur in patients who do not have apparent parotitis or orchitis. This suggests a possible explanation in certain cases of acute aseptic benign meningitis of unknown cause.

Echols, New Orleans.

Paroxysmal Trigeminal Pain with Tumours of the Nervus Acusticus. H. L. Parker, J. Neurol. & Psychopath. **17**:256 (Jan.) 1937.

Trigeminal pain is rare in association with tumors of the acoustic nerve. Of fifty-three cases, Parker found only four in which there was disturbance of the sensation of pain. He reports two more cases. Because of the rarity of the two conditions, their simultaneous appearance could not be regarded merely as coincidental. The pain was identical in all respects to that of tic douloureux and, as in the latter, could be relieved by injection of alcohol into the peripheral branches of the fifth nerve. Similar occurrence of trigeminal pain in cases of disseminated sclerosis has been reported in the literature. The explanation of such a condition is not yet clear. It has been suggested by Harris that the syndrome of both trigeminal and glossopharyngeal neuralgia is due to septic neuritis of the terminal filaments of the nerves caused by dental, tonsillar or sinus infections, and also that the condition may be inherited. Parker does not accept this view and is inclined to agree with Foerster that the condition is a state of functional hyperexcitability in the nerve apparatus, conditioned and facilitated by many and different causes. Parker draws analogies between this condition and that of facial spasm and believes that the underlying mechanism is the same in both conditions.

N. Malamud, Ann Arbor, Mich.

Atypical Effects of Tobacco in Cases of Disease of the Brain. E. Pappenheim and E. Stengel, Arch. f. Psychiat. **105**:623 (Nov.) 1936.

Pappenheim and Stengel describe the case of a woman aged 31, who experienced a parkinsonian syndrome several years after an attack of grip. Shortly before her admission to the hospital, she had attacks characterized by a compulsory desire to smoke. The smoking produced marked increase in salivation and sebaceous secretion and an increase in the rigor and tremors. The psychic concomintants of the attacks were much like postencephalitic compulsory states. It was shown that the choice of symptoms was definitely related to early fixations on an oral level. This suggestion of the possible anatomic substratum for such compulsory states following smoking was materially strengthened by the authors' experience in a case of tumor of the brain, the first symptom in which was a peculiar reaction to smoking, consisting of vertigo and attacks of abnormal sleep. Some time later, these symptoms began to appear without smoking. At autopsy a tumor was observed in the region of the midbrain. A third case is reported in which similar symptoms developed in a person suffering from exophthalmic goiter. These cases indicate that in patients suffering from lesions of the midbrain tobacco smoking is likely to exaggerate the symptoms, or even to cause them to become manifest when they are not otherwise clinically observable. It is interesting that the administration of nicotine did not produce the symptoms elicited by smoking.

Malamud, Iowa City.

THE CLINICAL AND PATHOLOGIC STATE IN CASES OF GLIOMATOUS METASTASES BY WAY OF THE SPINAL FLUID. G. BODECHTEL and K. SCHÜLER, Deutsche Ztschr. f. Nervenh. **142**:85 (Jan. 18) 1937.

Eight cases of glioma with metastases in the brain substance are reported. In only three of these were there clinical symptoms of metastasis. Certain symptoms are helpful in the diagnosis of metastases: (1) meningeal irritation; (2) impairment of the cranial nerves or spinal manifestations; (3) tumor cells in the spinal fluid; (4) vegetative disturbances, caused by a lesion of centers in the wall of the third ventricle, and (5) hematemesis, caused by acute hemorrhagic erosions of the stomach, presumably a sequela of central disturbances. Metastasis into the spinal subarachnoid space frequently causes no clinical symptoms. Metastasis is favored by diagnostic or therapeutic procedures in the brain. Metastases in organs of the body other than the brain do not exist, while propagation by way of the spinal fluid is frequent in cases of glioma. The histologic structure of metastases is different from that of the primary tumor and depends on the nature of the surrounding tissue.

ADLER, Boston.

ASPECTS OF PSEUDOBULBAR PARALYSIS (STRIOPONTILE FORM) IN YOUNG PERSONS. L. BINI, Deutsche Ztschr. f. Nervenh. **143**:158 (April 1) 1937.

Bini points out that in the literature cases are reported in which foci in the basal ganglia caused pseudobulbar paralytic manifestations. After citing some of these, he shows that in most cases of this condition there is in common a lesion on the external surface of the putamen, which partly involves the external capsule and the claustrum. The nucleus caudatus is less often involved. Occasionally the process spreads to the thalamus, and in rare cases also to the internal capsule. However, the characteristic aspects in these cases are the foci on the external surface of the putamen. These foci may produce the symptoms of pseudobulbar paralysis, even if the process in the putamen does not involve the capsule, the thalamus or the nucleus caudatus. It is also noteworthy that rigidity predominates in these cases and that they are related to the arteriosclerotic muscular rigidity described by Förster. In the majority of cases, including those observed by the author, there exist severe degrees of calcification of the vessels, so that the trophic factor plays a part in the genesis of the symptoms. A second group of cases of pseudobulbar paralysis concerns pontile foci, and they are usually of an arteriosclerotic nature. The author says that among the most interesting cases of pseudobulbar paralysis are those in which the basal ganglia or only the corpus striatum is involved. It has been suggested by some that in these cases the predominating condition is not so much paralysis as dystonia and parkinson-like symptoms. To such cases, however, the term pseudobulbar paralysis could not properly be applied. Nevertheless, in the older as well as in the more recent literature cases are reported in which the paralytic symptoms predominate over the striopallidal. Thus the question arises whether the striatum, in addition to its action on tonus, may not also influence motility. The author gives his attention to this question, on the basis of two case reports concerning men aged 45 and 44, respectively. In the discussion of these cases he points out that there is no reason to assume that the striatum has a motor, in addition to a tonic, function, for in the majority of cases of pseudobulbar paralysis in which the striatum showed a lesion other parts of the brain were also involved, such as the pons in one of his cases. The pontile involvement seems to indicate that in such cases the striatum exerts a modifying, not a determining, influence.

EDITOR'S ABSTRACT.

RESULTS OF DETERMINATION OF DIAMETER OF ERYTHROCYTES IN PATIENTS WITH HUNTINGTON'S CHOREA. F. VON DER MARK, Med. Welt **11**:41 (Jan. 9) 1937.

Von der Mark examined twenty-four patients with Huntington's chorea and detected enlargement of the erythrocytic diameter in twenty-one. He points out that this high incidence of enlargement of the erythrocytic diameter suggests the

possibility of a connection between Huntington's chorea and hepatic impairment. However, the literature reports only one case in which there were indications of such a connection. The author states further that the enlargement of the erythrocytic diameter in Huntington's chorea might suggest a connection with impairment of the bone marrow. On the other hand, he thinks that it may be merely a concurrence and not a relationship. EDITOR'S ABSTRACT. [J. A. M. A.]

PSEUDOHYSTERICAL COMPONENTS IN AN EXTRAPYRAMIDAL SYNDROME. M. I. ASTVATZATUROV, Probl. klin. i exper. nevropat. i psikhiat. **30**:27, 1936.

Astvatzaturov reports certain symptoms which he has observed in extrapyramidal conditions and which he believes demonstrate the close relationship between "organic" and "functional" disturbances. He describes a peculiar flexion contracture of the toes observed in six cases, with an occasional extension of the basal phalanges, a condition which interfered considerably with gait. The remarkable thing about the contraction was its inconstancy; while it increased when the sole of the foot was painfully stimulated, it disappeared when the dorsal surface of the foot was stimulated. Sometimes mere approach of the hand caused relaxation of the contracted toes. In another case of speech disorder of extrapyramidal origin, a command was sufficient to improve speech temporarily. On the basis of his observations, Astvatzaturov draws the conclusion that the old conception, according to which inconstancy and disappearance of symptoms under external stimulation are signs of the "hysterical" origin of symptoms, is incorrect and should be revised. He believes that the so-called hysterical symptoms may not only appear on a favorable soil already prepared by an organic condition but may be the result of an organic lesion of the brain, and this, according to him, proves once more the close relationship between the "somatic" and the "psychic" in the total organism. NOTKIN, Poughkeepsie, N. Y.

FLACCID HEMIPLEGIA IN ASSOCIATION WITH CEREBRAL NEOPLASMS. H. HOFF and O. PÖTZL, Probl. klin. i exper. nevropat. i psikhiat. **30**:50, 1936.

Hoff and Pötzl analyzed one hundred and seventy-nine cases of cerebral tumor and found only a few cases of flaccid paralysis of long standing. In none of these instances were signs of sensory involvement or evidence of increased intracranial pressure shown. In three cases there were malignant metastatic tumors in the opercular region. The flaccid hemiplegia was caused by pronounced collateral edema in the central region. The authors believe that the flaccidity in these cases was probably due to a tonus blockade caused by lesions in the various cerebral pathways. They believe that in these cases the corticifugal systems were more involved than the corticipetal, since the sensory functions remained intact. The pyramidal system was eliminated, while the corticothalamic system was in a state of continuous irritation, which, according to the authors, led to tonus blockade. This process, they believe, is, in a sense, the opposite of decerebrate rigidity. The fourth case was that of a parasagittal meningioma. The flaccid paralysis in this case is explained by prolonged and weak irritation, as evidenced by stretching of the thalamoparietal pathways. NOTKIN, Poughkeepsie, N. Y.

EPILEPSY OF HYPOTHALAMIC ORIGIN. H. NAKAGAWA, Psychiat. et neurol. jap. **41**:15 (April) 1937.

Nakagawa reports a case of measles encephalitis associated with epilepsy of hypothalamic origin. The patient, a boy, had an attack of measles at 6 years of age. Twenty days later, when the rash began to recede, there developed symptoms of extrapyramidal and hypothalamic involvement. These were ushered in by hypersomnia, followed a week later by psychopathic excitement, twitchlike movements of the body muscles, various compulsive states, peculiar postural anomalies and vegetative disturbances, such as severe salivation and increased secretion of

sweat. In addition, there were attacks characterized by rhythmic and painful flexion movements of the trunk without loss of consciousness, increased secretion of saliva and sweat and apnea followed by severe cyanosis. After these attacks there were decreased muscular tonus and sleep. These attacks occurred from five to twenty times a day and lasted from one to two minutes. The symptoms increased in severity as the disease progressed. After nine months the patient died. The blood and spinal fluid were normal. No autopsy is reported.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

CLINICAL AND ROENTGENOLOGICAL STUDY OF LOW BACK PAIN WITH SCIATIC RADIATION. C. E. BADGLEY, Am. J. Roentgenol. **37**:454 (April) 1937.

The striking preponderance of narrowing of the lumbosacral intervertebral disk, which occurred in 256, or 57 per cent, of his cases is to Badgley a significant factor in the production of the symptom complex. In 191 cases (43 per cent) the intervertebral joint space was normal. In the 73 cases included in this group in which there were normal roentgenographic signs, the same clinical phenomena were presented, except for less evidence of true neuritis, as demonstrated by disturbances in the achilles tendon reflex and sensory changes. The conclusion that superficial tenderness over the lumbosacral or sacro-iliac area is indicative of skeletal changes in the underlying joints seems to be questionable, in view of the fact that the relative frequency of this tenderness was the same in cases in which roentgenography showed a normal spine as in those in which abnormal roentgenographic changes appeared. It is the author's theory that pain low in the back with radiation into the leg is a clinical syndrome arising from a primary lesion in the lumbar, lumbosacral or sacro-iliac region, which is of muscular, joint or skeletal origin and produces radiation of pain by a referred mechanism which is typically postaxial in its distribution. The lack of evidence of true organic nerve injury in 79 per cent of cases is in favor of referred pain. The predominance of reflex and sensory changes in cases of narrowing of the lumbosacral disk suggests that in this type of lesion direct irritation of the nerve roots may develop in addition to the referred pain. The area of tenderness may also be the result of referred pain through irritation of the sensory nerves of the ligamentous structures rather than the indication of underlying pathologic changes in the joint. EDITOR'S ABSTRACT.

MYELITIS AND ENCEPHALOMYELITIS ASSOCIATED WITH GONORRHEA. LAMAN A, GRAY, Am. J. Syph., Gonor. & Ven. Dis. **21**:50 (Jan.) 1937.

Although only sixty-four cases of gonorrhea associated with myelitis or encephalitis have been reported, Gray thinks that the condition is probably much more common, as he collected five cases from the Johns Hopkins Hospital within a few years. The condition begins suddenly, with cerebral symptoms (coma or headache) or symptoms of involvement of the cord (incontinence or pains) two or three weeks after the acute gonococcic invasion. Improvement is slow, and when motor symptoms have developed, residual paralysis is likely. In every instance the attack of gonorrhea is severe. Of the sixty-four cases reported, sixty-one were in men, but in Gray's series of five cases only one occurred in a man. This patient, aged 26, had paraplegia, incontinence and anesthesia of the legs, which developed a month after the onset of acute epididymitis and gonorrhea. After two years he was able to walk fairly well.

Of the four women patients, only one had encephalitis. The other three showed areas of anesthesia, a loss of sphincter control and paraplegias, associated with a gonococcic pelvic infection. The fourth patient suddenly became comatose, three weeks after the onset of gonococcic salpingitis. She showed paralysis of the sixth, seventh and twelfth nerves and died twenty-two days after the first cerebral

symptoms. Autopsy disclosed widespread encephalomalacia in the white matter of the cerebellum and internal capsule, calcification of the walls of the smaller cerebral arterioles and numerous areas of necrosis in the brain. Gray believes that the gonococcus produces the changes in the central nervous system through the agency of an associated virus.

DAVIDSON, Newark, N. J.

LYMPHOGRANULOMA (HODGKIN'S DISEASE) WITH INVOLVEMENT OF THE SPINAL CORD. KARL O. VON HAGEN, Bull. Los Angeles Neurol. Soc. **2**:20 (March) 1937.

Von Hagen reports two cases of transverse lesion of the spinal cord due to lymphogranuloma. In the first, spastic paraplegia and sensory impairment below the fifth thoracic dermatome gradually appeared in a white man aged 24. Spinal puncture revealed clear, xanthochromic fluid, with block on jugular compression. A roentgenogram of the chest showed widening of the mediastinum. The diagnosis was confused by a positive Wassermann reaction of the blood and a pathologic report of tuberculosis in a cervical lymph node removed for biopsy. At operation a firm granulomatous mass was removed from the spinal epidural space; this was considered to be syphilitic because of the positive Wassermann reaction. During the next five months, however, a large firm mass appeared in the neck, and further roentgenograms of the chest showed a large tumor in the hilus and partial consolidation of the right lung. High voltage roentgen therapy resulted in marked reduction of the mediastinal tumor, and the diagnosis of lymphogranuloma was then made. The neurologic changes were unaltered.

The second case was that of a Negress aged 23, in whom spastic paraplegia and sensory impairment below the fourth thoracic dermatome gradually developed over a period of two weeks. Enlargement of cervical lymph nodes had been noted for two years. Roentgenograms of the chest showed widening of the mediastinum. On spinal puncture there was complete block and the total protein was estimated to be 61 mg. per hundred cubic centimeters of spinal fluid. High voltage irradiation produced steady improvement in the neurologic findings.

MACKAY, Chicago.

MYELOMALACIA WITHOUT THROMBOSIS FOLLOWING INDIRECT TRAUMA (STRAIN). LEO STONE and HARRY N. ROBACK, J. A. M. A. **108**:1698 (May 15) 1937.

Stone and Roback believe that their case is of special interest because of (1) the definite relationship of the condition to mechanical strain (the symptoms began while the patient was hanging by her arms from the limb of a tree) and (2) the unclear and stimulating problem of the precise pathogenesis. The strain suffered in this instance was not one that would ordinarily cause serious consequences, and this in itself raises the question of antecedent vascular or neural defect or concomitant infection. The postmortem conditions do not provide a basis for consideration of a specific antecedent defect. The patient was frail and anemic and had a chronic anal fistula. No evidence of syphilis could be demonstrated, nor was there definite evidence of other vascular disease. There was, furthermore, no evidence of venous or arterial thrombosis. The possibility of virus infection as an etiologic agent cannot be excluded in view of the clinical course, although the late anatomic changes offer no evidence of infection. The myelomalacia was (objectively) of characteristic ischemic type. The clinical syndrome presented by the patient was not that of the anterior spinal artery alone but rather a "transverse" syndrome, and anatomically the destruction of the posterior half of the cord was more nearly complete than that of the anterior half. The posture that the patient assumed was such that the whole subclavian system might have been thrown out of normal alinement. The authors think, therefore, that in a generally delicate and possibly definitely vulnerable person acute ischemia may have occurred on the basis of compression, angulation or even laceration of the lateral spinal arteries

or their parent trunks. The authors suggest that cases of slight or indirect trauma receive especially intensive clinical and anatomic study, that complete necropsies be performed when possible and that the vascular supply of the regions affected be dissected out up to the origins of the segmental arteries. This alone would settle conclusively some of the problems involved in this subject. EDITOR'S ABSTRACT.

TRANSVERSE LESION OF THE SPINAL CORD AT THE LEVEL OF THE FIRST AND SECOND LUMBAR VERTEBRAE AFTER CARBON MONOXIDE POISONING. HANS ZIPF, Deutsche Ztschr. f. Nervenh. **142**:39, 1937.

A patient who survived for about one day after attempted suicide with carbon monoxide showed, besides semiconsciousness and general disorientation, paraplegia of both legs, incontinence of the bladder and rectum, disturbance of all sensory qualities from the inguinal region downward and severe pain in the lower part of the back. Autopsy showed considerable swelling of the spinal cord at the level of the twelfth dorsal vertebra, and histologic examination revealed perivascular round cell infiltrations in this region. No sign of recent or older hemorrhage was seen in the cord or the lenticular nuclei. The carbon monoxide poisoning must therefore be regarded as the etiologic factor responsible for the clinical and pathologic picture. HOEFER, Boston.

NYSTAGMUS IN ASSOCIATION WITH TUMOR OF THE THORACIC PORTION OF THE SPINAL MEDULLA. H. HOFF and O. PÖTZL, Med. Klin. **33**:598 (April 30) 1937.

Hoff and Pötzl observed spontaneous nystagmus in three of six patients with a tumor in the thoracic region of the spinal medulla. They admit that because of the small number of cases the figures are of no significance, but they think that the characteristics of the nystagmus which appears in these cases deserve attention. They observed that it has a slow and a rapid component. The rapid component is in the direction of the visual movements; it is entirely horizontal and appears especially when the patient is standing or sitting or is in the abdominal or the dorsal position. Turning the pelvis or rotating the legs arrests the nystagmus. These seem to be the only movements that cause cessation of the nystagmus. To be sure, in one case completion of the lateral position was necessary to arrest it. After surgical removal of the tumor from the thoracic portion of the spinal medulla, the nystagmus disappeared completely, or only slight traces of it remained. As long as the nystagmus was at the peak of its development, pelvic movements toward either side and both lateral positions had the same effect, in spite of the fact that in the first two cases the spastic and the paretic conditions were not equally severe on the two sides. In evaluating the significance of the observations described, the authors point out that they indicate the need for a careful examination of the nystagmus that develops in cases of spinal tumor. Even if spontaneous nystagmus is absent, it is advisable to subject these patients to the same examination in order to determine whether some change in position might not elicit latent nystagmus. The differential diagnostic significance of this type of nystagmus is slight, because it occurs also in rare cases of multiple sclerosis; but it should be impressed on the nonspecialist in this field that the existence of nystagmus does not necessarily speak either against a tumor of the thoracic portion of the spinal cord or for multiple sclerosis. EDITOR'S ABSTRACT.

MYXEDEMA IN SYRINGOMYELIA. K. T. DUSSIK, Wien. klin. Wchnschr. **50**:372 (March 19) 1937.

Dussik states that the concurrence of myxedema and syringomyelia, both of which are comparatively rare, has been reported only once but that nervous disorders have repeatedly been observed in the ascendency in cases of myxedema. He himself observed a patient in whom classic myxedema developed many years

after syringomyelia had become manifest. It is noteworthy that the myxedematous changes developed at first in circumscribed areas that were most affected by the syringomyelia. In addition to the physical changes, there also developed mental disturbances. The memory became impaired; there was drowsiness; the thinking process was slowed down; the same thoughts and actions recurred, and there were frequent agoraphobic manifestations. In discussing the connections between the myxedema and the syringomyelia, Dussik suggests that a disturbance in the cervical portion of the sympathetic trunk, which developed in the course of the syringomyelia, may have impaired the sympathetic innervation of the thyroid. In this connection it is pointed out that syringomyelia has been known to concur with exophthalmic goiter. On the other hand, it is possible that central sympathetic factors might have played a part in the development of the myxedema. The author says that treatment with a preparation of thyroid produced favorable results in the case reported, in that the myxedematous symptoms disappeared. The symptoms of syringomyelia, however, remained unchanged. EDITOR'S ABSTRACT.

Peripheral and Cranial Nerves

THE GASTRIC ACIDITY IN ALCOHOL ADDICTS, WITH OBSERVATION ON THE RELATION OF THE B VITAMINS TO ACHLORHYDRIA. PHILIP M. JOFFE and NORMAN JOLLIFFE, Am. J. M. Sc. **193**:501 (April) 1937.

The gastric acidity curves for one hundred and five alcohol addicts, seventy-seven of whom were males and twenty-eight females, were studied. Inadequate secretion of free acid was found in 68 per cent (achlorhydria in 30 per cent) of the male subjects and in 71 per cent (achlorhydria in 35 per cent) of the female subjects. In each age group between the ages of 30 and 59, the frequency of achlorhydria exceeded the expected normal incidence. Pellagra was present in 26 per cent of the subjects, and achlorhydria occurred in 52 per cent of this group. Polyneuritis was present in 70 per cent of the subjects, 30 per cent of whom also had pellagra. Those with polyneuritis and without pellagra showed an incidence of achlorhydria of 29 per cent. Of twenty-six subjects who did not have pellagra or polyneuritis there was achlorhydria in 15 per cent, an incidence not significantly higher than would be expected in a normal group. There was greater retention of bromsulfalein in the pellagrins. The high frequency of achlorhydria in the alcohol addicts (three times the expected normal value) is thought not to be due to alcohol per se. It is pointed out that achlorhydria is associated with polyneuritis but is not due to vitamin B deficiency and that it is found with pellagra but is not due to a lack of the pellagra-preventive factor. The incidence of achlorhydria seems to vary directly with duration of the alcoholism. Achlorhydria is relatively common in alcohol addicts without vitamin B deficiency. Vitamin B is probably an achlorhydria-preventive factor.

MICHAELS, Boston.

PATHOLOGIC CHANGES IN MÉNIÈRE'S DISEASE. W. E. DANDY, J. A. M. A. **108**:931 (March 20) 1937.

In previous reports Dandy has shown that Ménière's and pseudo-Ménière's disease can be cured by section of the auditory nerve or, equally well, of the vestibular branch alone. The series of operations has now reached 170, in 160 patients, being bilateral in 10 instances. There has been no death and, except for early facial palsy in 4 cases, no after-effects from the unilateral operation. Like the cure for trigeminal neuralgia, that for Ménière's disease has antedated disclosure of the underlying cause. Since the disturbances do not in themselves produce death, pathologic material is scarce. The absence of necropsy material throws the burden of pathologic disclosures on conditions observed at operation. From this source a series of gross lesions in 8 cases is offered as the unequivocal cause of Ménière's disease. Only lesions of the sensory root of the auditory nerve (the vestibular division) can produce Ménière's disease, and consequently lesions in

the semicircular canals, such as concretions, are not a cause. However, although Dandy does not believe that concretions in the cochlear aqueduct can cause recurring attacks of dizziness and loss of hearing, he is not able to make a categorical denial that they may do so. The effects of irritative or occlusive concretions in this channel are not yet known. It would be difficult, however, to understand how an occlusion in the ductus cochlearis could affect the semicircular canals, which, although connected through the ductus endolymphaticus, should be independent of any secondary effect from an obstruction. Concerning the theory of Portmann and Aboulker, that pressure effects are transferred from the cisterna lateralis through the ductus endolymphaticus, one can be positive. That pressure in the lateral cistern does not in any way affect the semicircular canals or the organ of Corti is easily shown by the absence of effect in the great number of cases of tumor of the brain in which it is known that an increase of pressure in the lateral cistern is always produced. There is never any pathologic effect on hearing or vestibular function. Such a conception is purely fanciful, without any anatomic background. Nor in a single operative exposure of the lateral cisterns in this series has there been observed any abnormality; certainly, there has been nothing suggestive of localized meningitis, which is an almost impossible conception.

EDITOR'S ABSTRACT.

PERIPHERAL NEURITIS AS A SEQUEL TO SUN-BATHING. JAMES HANNAN, Brit. M. J. **1**:73 (Jan. 9) 1937.

A woman aged 29 awoke with pain in the ankles and paralysis of the legs on the day following a sun bath of six hours' duration. The knee jerk and plantar reflex were absent on both sides, and there was loss of epicritic sensation over the outer sides of the legs and feet. The temperature and pulse were normal, and there was no evidence of other disease. Foot drop was present bilaterally after twelve days, but the patient eventually recovered.

ECHOLS, Ann Arbor, Mich.

LUMBAGO AND SCIATICA. A. H. DOUTHWAITE, Lancet **2**:326 (Aug. 8) 1936.

Douthwaite states that the terms "lumbago" and "sciatica" have been used loosely and often indicate a symptom rather than a disease. Sciatica implies pain in the course of the sciatic nerve, irrespective of cause. Lumbago should be considered as fibromyositis of the lumbosacral region, occurring in acute or chronic form. Acute lumbago comes like a bolt from the blue. At one moment in good health, at the next the victim is stricken with a fierce pain in the back which holds him in a position of agonized rigidity. The muscles in the affected area are diffusely tender, but as a rule one spot can be discovered at which deep pressure produces exquisite pain. It is more or less generally accepted that fibrositis of this type is due to local failure of circulation to remove the waste products of muscular contraction. With correct treatment, acute lumbago can be expected to disappear in from three days to a week. On rare occasions, when a patient has sufficient courage to perform vigorous spinal exercises in spite of pain, great, and sometimes complete, relief is obtained in half an hour. As a rule, however, one must rely on other means, the most effective of which is thorough muscular kneading two or three times a day. Subsequent to this deep massage, movement is always easier and should then be encouraged in the form of brisk spinal exercises for a short period. Thereafter prolonged heating with a thermopad or very hot water bottles and rest in bed will obtain the quickest results. The use of analgesics, such as acetylsalicylic acid, may influence the course of the disease favorably, for, by relief of pain, they allow the all important active movements of the trunk. The most favorable prognosis may be completely upset by the development of sciatic pain after a day or so of pure lumbago. Chronic lumbago, which tends to follow a series of acute attacks, is characterized by constant discomfort and stiffness in

the back, giving place from time to time to short outbreaks of acute pain. The commonest demonstrable organic disease mistaken for chronic lumbago is osteoarthritis of the spine. No patient with apparent chronic lumbago should be treated before roentgenologic examination of the spine has been made. The outlook is good in a case of chronic lumbago in which the spine is relatively healthy. All that is needed is manipulation of the back under anesthesia, followed by deep massage and active spinal exercises. Complete recovery in two months is the rule. The prognosis for chronic lumbago with spinal arthritis must be guarded. The most potent predisposing cause of acute lumbago is the vague condition of being "run down."

Douthwaite states that what is commonly called sciatica may be either sciatic neuritis or central sciatica. It would be better if the term "sciatica" were reserved for acute sciatic neuritis. In this condition there is unilateral pain in the course of the sciatic nerve, associated with tenderness of the nerve at various points, diminution or loss of the ankle jerk, a similar modification of sensation, especially on the outer side of the foot, sole and ankle, acute pain on stretching the nerve and some loss of power in the muscles of the legs, especially those producing dorsiflexion. Sciatic neuritis follows acute lumbago with great frequency, and presumably the same "rheumatic" process is responsible for the two conditions.

First and foremost, organic disease simulating sciatica must be excluded. No case of sciatica has been studied adequately without a roentgenologic examination of the lumbosacral portion of the spine and the pelvis, hip joint and upper half of the femur. Neither may a rectal examination or general overhaul be omitted. Any patient with sciatic pain in both legs must be suspected of central—e. g., vertebral, spinal or pelvic—disease, with the real possibility of a tumor of the cauda equina not being forgotten. In short, when all other investigations in such cases prove negative, examination of the cerebrospinal fluid is imperative before the diagnosis of bilateral sciatica is accepted.

Sciatic neuritis having been established, the prognosis is six weeks in bed and an additional four weeks before return to any hard physical work. If the patient lies flat on the back with the limb immobilized by means of sandbags and towels, recovery usually follows. Diathermy, manipulation, injections or stretching the nerve are harmful, and Douthwaite says that there is no such thing as a dramatic cure in true acute sciatica.

On the assumption that general causes, such as gout, gross focal sepsis and constipation, have been dealt with, the usual explanation for persistence of chronic sciatic neuritis is the presence of adhesions between the nerve and the surrounding structures and the nerve sheath and its contained nerve bundles. Another cause is persistence of lumbosacral fibrositis, which often initiates an attack. If evidence of lumbago is still found, treatment must be directed to this condition. If this fails, the stage has been reached for closed stretching of the nerve under anesthesia and for injection of saline. These measures produce prompt relief in about one-half the cases. In every case of sciatica and of lumbago, the posture must be corrected if recurrences are to be avoided.

Central sciatica denotes a condition in which sciatic pain is felt down one limb but in which the cause is a lesion of indeterminate nature in the region of the lumbosacral vertebrae. The trouble, therefore, does not include gross lesions, such as malignant deposits or fractures. The signs differ from those of sciatic neuritis in that the ankle jerk is seldom affected, there is no tenderness of the nerve and any sensory loss is slight and usually limited to the extreme outer border of the foot. On the other hand, there is usually tenderness of the erector spinae muscle close to the corresponding sacro-iliac joint, tenderness over this joint or limitation of movement of the lower part of the spine. The two common causes are strain and recurrent fibrositis of the lumbosacral region. Acute central sciatica, when due to strain, provides opportunity for dramatic cure. It is here that a single manipulation may banish pain which has been present for weeks. In chronic central sciatica the prognosis is also good. Manipulation of the spine, deep massage, exercises and epidural injection of saline are right measures to adopt. If these

are carried out adequately, complete recovery can be anticipated in over 80 per cent of cases. Chronic backache and chronic central sciatica are essentially diseases of middle age. They are bound up with the entirely unnecessary increase in girth and decrease in spinal movement common at this age.

WATTS, Washington, D. C.

INTRACRANIAL SECTION OF THE AUDITORY NERVE IN TREATING AURICULAR VERTIGO. M. OMBRÉDANNE, Mém. Acad. de chir. **63**:379 (March 17) 1937.

Ombrédanne utilizes Dandy's method in a modified form: partial section of the auditory nerve, which suppresses vertigo and pain but saves the sense of hearing. In all of nineteen cases of simple Ménière's syndrome in which operation was performed, the result was successful. Of seventeen patients with atypical Ménière's syndrome, fourteen were cured; two died, and in one the symptoms persisted. Some of these patients were very vertiginous and deaf in one ear and had intolerable tinnitus. The two who died had chronic otorrhea and had previously had several operations. The patient is prepared with sedatives a few days before the operation. He is made to lie on his abdomen, with his head beyond the border of the table on a special support. With the area under local anesthesia, the incision is started about 1½ inches (3.8 cm.) below the external occipital protuberance near the median line, runs obliquely toward the posterosuperior angle of the mastoid and goes straight down to the inner side of the apex of the mastoid. When the zone is exposed, care must be taken of the mastoid vein and of the subcccipital venous plexuses. The trephine opening is made with a large drill in the horizontal part of the occipital bone, about an inch (2.5 cm.) from the posterior border of the mastoid and from the upper curved line of the occipital bone. The orifice is then rapidly enlarged by means of semicircular forceps, but cautiously, lest the mastoid cells be opened. With the aid of a small hook, the dura is drawn back from the cerebellum as much as possible and a crossed incision is made resulting in four flaps. The postero-inferior aspect of the cerebellum is then raised. The arachnoid over the posterior cistern is incised. A retractor is then inserted between the petrous bone and the cerebellum, and the latter is pushed slowly inward while the retractor is gradually forced deeper. Evacuation through suction of the ponto-cerebellar cistern gives access to the auditory nerve. The two branches of the auditory nerve are separated, and the thicker, the vestibular, nerve is cut. Its two ends recede immediately, leaving the cochlear nerve intact. The dura is then carefully sutured with fine catgut or silk, and a drain of horsehair is left between it and the skin flap for from twenty-four to forty-eight hours. Among the post-operative events may be mentioned violent nystagmus, which disappears in from ten to twenty days, and vomiting and vertigo, which vanish soon. The same may be said of the occipital headache, elevation of temperature (100.4 F.) and diplopia. But the original pain, dizziness and tinnitus, so strong at the time of the operation, do not return.

EDITOR'S ABSTRACT.

POLYRADICULONEURITIS ASSOCIATED WITH HYPERALBUMINOSIS OF THE CEREBROSPINAL FLUID WITHOUT CELLULAR REACTION AND WITH OPTIC NEURITIS (GUILLAIN-BARRÉ SYNDROME). DUMOLARD, SARROUY, SCHOUSBŒ and BADAROUX, Rev. d'oto-neuro-opht. **15**:26 (Jan.) 1937.

The case reported is that of a man aged 26, who was suddenly attacked by weakness of the lower limbs, accompanied by numbness, formication and coldness of the feet, calves and thighs. Examination revealed hypesthesia to touch and prick in the hands and feet, pain on pressure on the muscle masses, lack of power in the muscles of the limbs, loss of osteotendinous and cutaneous abdominal reflexes and flaccidity of the muscles. All cranial nerves except the optic were normal. Mixed strabismus and alternating convergent strabismus had existed since birth. Examination of the eyegrounds revealed bilateral optic neuritis, contraction of the visual fields, especially for red and green, and reduced visual acuity: visual acuity

was 4/10 on the right and 2/10 on the left with correction. The Wassermann reactions of the blood and spinal fluid were negative. One month's stay in the hospital resulted in marked improvement in the condition, although atrophy of the optic nerve remained stationary. Excessive indulgence in alcohol had been practiced for several years prior to admission. Involvement of the optic nerves in the Guillain-Barré syndrome is exceptional. It is to be attributed in this case to the previous condition of the eyes and to the excessive use of alcohol.

DENNIS, San Diego, Calif.

A CASE OF ACUTE PRIMARY INFECTIOUS POLYNEURITIS. M. NAKAYA and K. NISHIMURA, Psychiat. et neurol. jap. **41**:1 (Jan.) 1937.

The syndrome described by Nakaya and Nishimura is known as the Guillain-Barré syndrome and has also been designated as acute primary infectious polyneuritis. The case reported was that of a chauffeur aged 23, who complained first of a feeling of ill-being, pain in the neck and limbs and fever. He noticed twitchings in both shoulder girdles and arms, followed a few days later by disturbances in motion and sensation and weakness of the right leg and left arm. There was a steppage gait. There was hypesthesia over the entire left shoulder to the left arm, anteriorly below the umbilicus and posteriorly below the fifth lumbar vertebra. There was no disturbance of deep sensation. The patellar and achilles reflexes were absent. There were 17 cells per cubic millimeter of spinal fluid. The Wassermann reactions of the blood and spinal fluid were negative. After a month there was atrophy of the muscles of the left shoulder girdle and arm and the right pelvic girdle and leg. Gradual improvement in motion and sensation took place, so that after two months movement of the left arm was almost normal; the sensory disturbances of the left arm had disappeared, and the patient had practically recovered.

ALPERS, Philadelphia.

Vegetative and Endocrine Systems

EFFECT OF THYROID THERAPY ON THE MENTAL AND PHYSICAL GROWTH OF CRETINOUS INFANTS. A. GESELL, C. S. AMATRUDA and C. S. CULOTTA, Am. J. Dis. Child. **52**:1117 (Nov.) 1936.

The authors studied six cases of cretinism in which the condition was recognized and adequately treated in infancy, in an effort to determine the effect of therapy on the physical and mental status. Physical improvement occurred in all cases, with loss of the cretinous facies and habitus and acceleration in physical growth, especially in the length of the legs. The indicators used to gage the growth of the central nervous system were the reaction patterns of the infant in the fields of posture, locomotion, prehension, language and adaptive and social behavior, their maturity values being expressed in terms of the developmental quotient. In two patients studied the mental status remained defective, while in four it was lifted above the zone of mental deficiency.

Prognostic clues to the physical and mental development are revealed in the immediacy of the therapeutic response. A quick initial gain augurs a large total gain; the more delayed the initial gain the smaller the total increment. The first two years of treatment are of critical importance in both the physical and the mental gain.

While the primary effect of thyroid therapy is on the thyroid gland itself and on associated glands, its final effect on the cretin is contingent on the residual physiologic capacity and latent growth potency of his neuroendocrine system. Thyroid therapy cannot bring about normality if there has been fundamental impairment of that system—hereditary or developmental. The initial response to treatment is an index of the reserve capacity of the neuro-endocrine system.

WAGGONER, Ann Arbor, Mich.

A Clinicopathologic Study of Sexual Precocity with Hydrocephalus. G. B. Dorff and L. M. Shapiro, Am. J. Dis. Child. **53**:481 (Feb.) 1937.

The cases of two female children presenting chronic hydrocephalus, spastic paralysis of the legs and macrogenitosomia praecox are described. Autopsy in one case, after death from pneumonia fifteen days after ventriculography, revealed internal hydrocephalus, cortical atrophy with marked atrophy of the mamillary bodies, chronic ependymitis, sclerosis of the basal portion of the leptomeninges, physiologic hyperplasia of the breasts and ovaries, microcystic degeneration of the ovaries and a miliary adenoma of the right adrenal gland. There was a small remnant of the pineal gland. The pituitary body was slightly enlarged and compressed but was apparently normal histologically. The hypothalamus was thin and atrophic, but the hypothalamohypophysial pathway was intact. Dorff and Shapiro suggest that chronic increased intracranial pressure with compression of the hypothalamo-infundibulohypophysial pathway was the starting-point for development of the sexual precocity.

Waggoner, Ann Arbor, Mich.

The Relation of the Basophilic Cells of the Human Hypophysis to Blood Pressure. A. T. Rasmussen, Endocrinology **20**:673 (Sept.) 1936.

Study of the relationship between the basophilic cells of the hypophysis and arterial hypertension has been productive of conflicting evidence. Rasmussen compared the amount of epithelium in the pars intermedia of thirteen greatly overweight women and of twenty-two men weighing 200 pounds (90.7 Kg.) or more with that of two hundred normal women and men who were not excessively fat. The results show a distinctly greater amount of epithelium in the obese group, which was largely, if not entirely, due to an excess of basophilic cells. Rasmussen believes that the relationship between the basophilic cells of the hypophysis and elevated blood pressure is far from proved. The coefficients of correlation between blood pressure and the relative number of basophils in the anterior lobe and between blood pressure and the amount of epithelial tissue in the region of the pars intermedia are essentially zero. Differences based on age and sex are, however, significant. The accumulation of basophilic cells in the posterior lobe increases slowly with age; while blood pressure also tends to rise with age, the one is not necessarily the cause of the other. Three cases of pituitary basophilism are added to those already reported in the literature. The characteristic hyaline change in the cytoplasm of basophils of the anterior lobe was shown, regardless of whether there was a pituitary adenoma or an adrenal neoplasm or neither. These hyaline changes occur only rarely, and then only to a slight degree in essential hypertension, eclampsia and other conditions with high blood pressure unaccompanied by the typical clinical picture of pituitary basophilism.

Palmer, Philadelphia.

Light in Its Relation to Activity and Estrous Rhythms in the Albino Rat. Ludvig G. Browman, J. Exper. Zoöl. **75**:375 (April) 1937.

Light is known to affect reproductive organs or activity rhythms in a number of mammals. Mature female albino rats were studied under various conditions of illumination. It was found that the daily activity rhythm of rats exposed to continuous light is a periodic fluctuation (from five to six days) between nocturnal and diurnal activity. Reversal of day-night light conditions causes a reversal of daily activity rhythms. In constant darkness rats tend to keep the rhythm with which they entered the period of darkness. Normal estrous cycles were exhibited in continuous darkness, in reversed day-night conditions and in ordinary daylight, but in continuous light prolonged vaginal cornification occurred. Rats with the lens and humor of both eyes removed, without injury to the retina, reacted in the same way as normal animals. Rats that were blinded by removal of both eyeballs or by severance of the optic nerves maintained nocturnal activity rhythms and normal estrous cycles regardless of light conditions. Animals blinded during

"light estrus" quickly returned to normal cycles. All day exposure to early summer sunlight for seven weeks did not induce "light estrus." Constant auditory stimuli for four weeks did not influence the estrous or activity rhythms. Three generations of rats raised under continuous light showed no significant differences from a closely related strain of rats kept under colony conditions in regard to time of puberty or age at the first litter from brother-sister matings.

WYMAN, Boston.

THE RELATION OF THE PITUITARY TO LIVER GLYCOGEN PRODUCTION AND UTILIZATION. OLIVER COPY, J. Physiol. **88**:401, 1937.

Rabbits from 6 to 8 weeks of age were hypophysectomized through the nasopharynx and base of the sphenoid bone. Diminished endogenous production of carbohydrate, first observed by Houssay, was observed consistently. The importance of the liver in the control of the sugar level of the blood was demonstrated. In the fasting state the level of the blood sugar is maintained until the glycogen in the liver is almost completely depleted. This loss of glycogen from the liver occurs in a few hours and is followed by a rapid fall in blood sugar to convulsive levels, in a manner similar to that observed in the hepatectomized rabbit. Utilization of dextrose is not impaired, and glycogen is readily stored in the liver from dextrose given intravenously. Epinephrine and insulin do not cause storage of glycogen in the liver, as they do in the normal animal. The failure to maintain the liver glycogen and blood sugar is not due to a diminished quantity of glycogen in the muscle.

McCOUCH, Philadelphia.

CHANGES IN THE ENDOCRINE GLANDS FOLLOWING LESIONS IN THE DIENCEPHALON. MARES CAHANE and TATIANA CAHANE, Rev. franç. d'endocrinol. **14**:472 (Dec.) 1936.

Cahane and Cahane produced atrophy of the genital apparatus without adiposity by means of experimental lesions in the diencephalon and then took up the task of localizing the center responsible for the changes. For this purpose, they made careful anatomic studies of the brains of four cats in which they produced the genital syndrome. This study revealed a section through the hypophysial stalk in one cat and amputation of the stalk and occlusion of the infundibular recess in another. In a third cat the preparations showed a puncture through the infundibular floor, with hemorrhage into the lateral ventricles. In the fourth cat the experimental lesion destroyed parts of the optic chiasm and the supra-opticohypophysial bundles. The authors counted and measured the size of the cells in the supra-optic nuclei in the four brains and compared them with the observation in four brains used as controls. In the animals serving as controls there were 56 cells in sixteen squares, the sizes of which ranged from 15 by 10 to 10 by 6 microns, while in the animals on which operation had been performed there were 54 cells measuring from 17 by 8 to 8 by 7 microns. The cells measuring 8 by 7 microns were the most prevalent. While the authors saw no definite evidence of lesions in the supra-optic nuclei they believe that they produced a lesion in the supra-opticohypophysial pathways. This pathway carries impulses which regulate the gonadotropic secretion of the anterior lobe, since lesion of this tract produced atrophy of the genital apparatus.

The authors studied also the effect of diencephalic lesions on the endocrine apparatus in five male and five female rats, in six of which there developed the syndrome of genital atrophy without obesity. They report in detail the changes seen in a male animal, as compared with those observed in an animal used as a control. The animal on which operation was performed lost 29 Gm. in four months, while the control animal gained 61 Gm. in five months. The thymus, spleen and adrenals of the animal undergoing operation weighed more than those of the normal animal, while the thyroid, liver, kidneys and genital organs were heavier in the normal animal. The pancreas in both animals was of about the same weight. Histologic examination showed complete arrest of

spermatogenesis. In a female rat on which operation was performed the uterus and the uterine horns were infantile in size and shape, and the ovaries were atrophied. Histologic examination showed a generalized atrophic process. The anterior lobe of the pituitary showed rarefaction and reduction of the protoplasm in the cells and decrease in the number of eosinophilic and cyanophilic cells; the nuclei were eccentric, with many vacuoles, and stained poorly. There were also reduction in the chromatin substance and disappearance of the nucleolus. Histologic changes were also noted in the posterior lobe and in other endocrine glands. The authors concluded that, while there exists a center in the anterior lobe which regulates the secretion of the gonadotropic hormone, they were unable to localize a similar center in the diencephalon. They believe that the syndrome of genital atrophy is probably due to the physiologic changes in the anterior lobe of the pituitary gland.

NOTKIN, Poughkeepsie, N. Y.

Treatment, Neurosurgery

THE THERAPEUTICS OF PROSTIGMIN: A WARNING CONCERNING ITS ORAL USE BASED ON A PERSONAL EXPERIENCE. L. S. GOODMAN and W. J. BRUCKNER, J. A. M. A. **108**:965 (March 20) 1937.

There is no doubt in the minds of Goodman and Bruckner that the case which they report is one of severe poisoning due to prostigmin (the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate). All the classic signs of physostigmine intoxication were present. The heart rate fell within thirty minutes after the drug was taken and reached its lowest level in one and one-half hours. Thus, vagus nerve endings in the heart appear to be more sensitive to the drug than other parasympathetic nerve endings. The change in the heart rate also indicates that no delay occurred in the absorption of the drug. Salivation was not noted until one and one-half hours after the drug was taken, and only after the heart rate was maximally slowed. The long latent period (ninety minutes) between salivation and sudden onset of shock and activity of the intestinal and skeletal muscle is important because it indicates that full action of the drug was not manifested for three hours after ingestion, despite definite evidence that absorption began early. The reason for the onset within a few seconds of severe signs and symptoms is unexplained. Either the rate of absorption was suddenly increased, which appears unlikely, or, after gradual absorption, the concentration of the drug reached the toxic level. Another possibility is that there was an undue accumulation of acetylcholine from the activity of voluntary muscles during the brisk walk home and that the prostigmin, by preventing its destruction, allowed the acetylcholine to cause poisoning. The shock picture resembled somewhat that seen in cases of an overdose of acetylcholine, except that the skeletal muscles were involved and there was no cutaneous vasodilatation. Muscles which are most involved in myasthenia gravis—the extra-ocular muscles and muscles of the eyelids, face, lips, tongue, throat and neck—still contracted after other muscle groups had ceased, and were most painful during the following forty-eight hours. Persistence of consciousness during physostigmine poisoning was also noted in this case. The spasm of accommodation and the miosis were typical. Oddly, no lacrimation was observed, although the sudden, short spell of nasal discharge may in reality have been due to tears. The pulse, slow in proportion to the degree of shock and the evidently low blood pressure, was characteristic of this type of poisoning. Atropine is a specific physiologic antagonist, and the relief it brought in this case is clear. If prostigmin is needed in treatment for myasthenia gravis, the authors suggest that for the present it be given parenterally, so that the dosage can be controlled. If this is impossible, it seems wisest to rely on other therapeutic measures until more is known concerning the oral use of prostigmin. Any claims that prostigmin is less toxic for man than physostigmine and has a higher therapeutic index should be reserved until more clinical evidence is available.

EDITOR'S ABSTRACT.

USE OF BENZEDRINE SULFATE IN POSTENCEPHALITIC PARKINSON'S DISEASE. P. SOLOMON, R. S. MITCHELL and M. PRINZMETAL, J. A. M. A. **108**:1765 (May 22) 1937.

Solomon, Mitchell and Prinzmetal used benzedrine sulfate in conditions in which asthenia is a prominent symptom. Twenty-eight patients with postencephalitic Parkinson's disease, ten patients with arteriosclerotic Parkinson's disease and twenty-two patients with psychoneurosis were given benzedrine sulfate for periods varying from four weeks to sixteen months. Beneficial effects from benzedrine alone, or from the addition of benzedrine to scopolamine or stramonium, were reported by twenty-six (93 per cent) of the twenty-eight patients suffering from postencephalitic Parkinson's disease. The most uniform result was that of a feeling of increased energy and well-being. This was remarked by twenty-five of the twenty-six patients in whom lack of energy was a symptom. Drowsiness and the necessity for frequent naps during the day were also eliminated in twenty-three of the twenty-four patients in whom these symptoms were found. Improvement was noted in only fifteen (53.6 per cent) of the twenty-eight patients when benzedrine was used alone; in two of these the improvement was felt to be equal to the effect from the combination of benzedrine with scopolamine or stramonium; in both these cases, lack of energy and drowsiness were the outstanding symptoms. Of the ten patients with the arteriosclerotic type of Parkinson's disease who received benzedrine, six were worse; the condition of three remained unchanged, and one felt better. When benzedrine was added to scopolamine or stramonium, two of six patients felt worse; the condition of three was unchanged, and one felt better. The one patient who felt better in each instance had only mild symptoms and was benefited also by blank tablets. Of the nine patients who were not benefited by benzedrine, seven were helped by scopolamine, while the condition of the other two was not improved by any medication. The untoward effects noted in the six who were made worse by benzedrine were: insomnia, in all six; restlessness and irritability, in four; increased tremor, in three; anorexia, in three, and nausea and vomiting, in two. In only two of the twenty-two selected patients with various forms of psychoneurosis, whose chief complaints were also lack of energy, drowsiness, weakness and easy fatigue, was there definite subjective improvement in asthenic symptoms, as compared with the improvement noted in 93 per cent of the postencephalitic group. The improvement in the patients who were benefited by benzedrine was controlled by the substitution of blank pills. The usual maintenance dose of benzedrine sulfate was from 10 to 20 mg., taken orally two or three times a day. In one patient 5 mg. twice a day was the optimum dose. As much as 160 mg. a day for three weeks was taken by one patient without apparent harmful effect. Usually 5 or 10 mg. was given before breakfast and before lunch and the dose increased gradually until the maximal therapeutic effect was obtained. Scopolamine hydrobromide, from $\frac{1}{200}$ to $\frac{1}{100}$ grain (0.3 to 0.6 mg.), or stramonium leaves, from $2\frac{1}{2}$ to 5 grains (0.16 to 0.32 Gm.), was given two or three times a day, both in combination with benzedrine, in most cases, and alone, in an attempt to determine the most effective regimen. The duration of action of an individual dose of benzedrine varied from three to seven hours, though most patients reported that beneficial effects began to wear off in four or five hours. Patients, particularly those with oculogyric crises, felt the effect of benzedrine in from fifteen to twenty minutes.

EDITOR'S ABSTRACT.

TWO CASES OF STREPTOCOCCIC MENINGITIS TREATED SUCCESSFULLY WITH SULFANILAMIDE AND PRONTOSIL. M. H. WEINBERG, R. R. MELLON and L. E. SHINN, J. A. M. A. **108**:1948 (June 5) 1937.

Weinberg, Mellon and Shinn used sulfanilamide and a derivative called prontosil-soluble (the disodium salt of 4-sulfamidophenyl-2′, azo-7′-acetylamino-1′-hydroxy-naphthalene-3′, 6′-disulfonic acid) in two cases of streptococcic meningitis. They also studied its effects in comparison with those of a new type of serum treatment

which has been used successfully by them for nearly a decade. Of the two cases, the second is the one that merits the greater attention. The patient was practically moribund when she was admitted. From both the clinical and the bacteriologic standpoint the child appeared to be doomed. She had marked bulbar involvement, and the dysphagia was almost complete. There is no reasonable doubt that a noteworthy bacteriostatic, and probably a bactericidal, effect of the spinal fluid is present. It is particularly clearcut in the second case, in which no growth of streptococci occurred after treatment, despite the fact that ten times the original inoculation was employed. The relative sparsity of streptococci present in the smears supported this observation. It was found that when 125 of the patient's streptococci were incubated in the patient's fresh spinal fluid, about half of them refused to grow after eight hours' incubation at 37 C. After twenty-four hours none grew. Of the ultimate fate of these inhibited or killed organisms in the human being, little is known. The question of dosage and method of administration cannot be answered definitely as yet. Sulfanilamide does not seem to be toxic, so it is rather safe to use. Attempts at standardization of dosage are already being made. The authors have given normal persons as much as 4 Gm. a day, and their patients with type III pneumonia, who have shown a remarkable response (recovery in about 75 per cent) have often received as much, and sometimes more, daily. When swallowing is difficult the drug should be given intramuscularly. The authors have overcome the difficulty of the patient's inability to swallow the tablet by administering the drug by rectum. Therapy should be started immediately. The bacteriostatic observations of the English workers estimate that it takes at least forty-eight hours before such effects can be obtained in the serum, and because of this the treatment should be instituted promptly. In their second case the authors started the treatment in one hour and twenty minutes, the time that it took to complete the neurologic examination, the lumbar puncture and the microscopic examination of the fluid after admission of the patient to the hospital.

CLINICAL OBSERVATIONS ON THE EFFECT OF BENZEDRINE SULFATE: A STUDY OF PATIENTS WITH STATES OF CHRONIC EXHAUSTION, DEPRESSION AND PSYCHONEUROSIS. D. L. WILBUR, A. R. MACLEAN and E. V. ALLEN, J. A. M. A. **109**:549 (Aug. 21) 1937.

Wilbur, MacLean and Allen consider the effects of administration of benzedrine sulfate to one hundred patients during a short time and to forty-four patients during periods varying from two weeks to eight months. Careful examination of all these patients revealed no detectable evidence of organic disease. The drug was administered orally, in the form of the sulfate, in doses of from 2.5 to 20 mg. before breakfast, and frequently the dose was repeated at noon. A placebo tablet, identical in appearance with that which contained benzedrine, was administered on occasions and failed regularly to cause any change of symptoms. Although the initial results that follow the administration of benzedrine to patients who are in states of chronic exhaustion and depression are favorable in a high percentage of instances, it is obvious that continued use of the drug lessens its effectiveness. The studies show that although the initial effects of the administration of benzedrine are beneficial to from about 70 to 80 per cent of patients in states of exhaustion that are not due to organic disease and to about the same percentage of patients in states of depression, the percentage of favorable effects decreases significantly if administration of the drug is continued for weeks or months. This is in sharp contrast to the results of the treatment for narcolepsy. Observations over longer periods than those reported may show still further limitation of the use of benzedrine. Benzedrine is a stimulant and therefore apparently does not fundamentally and permanently alter a psychotic disorder or a state of chronic exhaustion. Whether it is logical and safe continuously to stimulate patients who present such disturbances cannot be answered at present. EDITOR'S ABSTRACT.

INSULIN SHOCK TREATMENT OF SCHIZOPHRENIA. E. H. LARKIN, Brit. M. J. **1**:745 (April 10) 1937.

All the patients with schizophrenia treated by Larkin with the daily insulin shock method have had an advanced stage, with marked symptoms of dementia praecox. Five patients have completed treatment. Three have apparently recovered. The other two are still being watched, their insight being developed by daily talks with a view to their adapting themselves well to life when they shall have returned to the outside world. Of the two who have not recovered, one is greatly improved and the other is unchanged. All except the one patient for whom the treatment was not beneficial have put on weight while actually under treatment. A sixth has already lost his delusions and hallucinations, after an unremitting attack lasting eighteen months.

EDITOR'S ABSTRACT.

LUMBAR SYMPATHECTOMY AS TREATMENT FOR POTT'S PARAPLEGIA. I. JIANO, Z. IAGNOV and G. TIMUS, Presse méd. **45**:508 (April 3) 1937.

Encouraged by Diez' reports (1929), Jiano and his associates performed two lumbar sympathectomies in cases of advanced Pott's disease with paraplegia. In both cases typical motor, reflex and tactile disorders were shown. Roentgenograms in both showed partial destruction of lumbar vertebrae. A right lumbotomy was done with the patient under ether anesthesia. The sympathetic chain was found between the vena cava and the spinal insertion of the psoas muscle. In this operation the sympathetic chain is isolated by means of small tampons; the communicating branches are sectioned, and the sympathetic chain is extirpated, together with the second and third lumbar ganglia. No drain is necessary on closing. Twenty-four hours later the patient is able to move the toes and both feet. On the next day the legs can be flexed. Gradually, the amplitude of the movements increases; the reflexes become lively, and the Babinski reflex is negative. About two weeks after the operation the patient can keep upright when supported and can even take a few steps. After three months all functions are restored. Owing to persisting vertebral pains, an osteosynthesis was done in one case. The intervention directed against the sympathetic chain determines a physiologic modification in the vascular provision for the spinal cord. Healing of the paraplegia is then explained by the coming into play of a system of arterial anastomoses, even when the seat of the vertebral lesion is above the level of the sympathectomy.

EDITOR'S ABSTRACT.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

FREDERICK H. ALLEN, M.D., *President, in the Chair*

Regular meeting, Oct. 8, 1937

SYMPOSIUM ON THE INSULIN TREATMENT FOR SCHIZOPHRENIA

STATISTICS ON INSULIN SHOCK THERAPY FROM THE PENNSYLVANIA HOSPITAL DEPARTMENT FOR MENTAL AND NERVOUS DISEASES. DR. DONALD HASTINGS.

Therapy has been completed in 41 cases, the duration of treatment being from six to seven weeks or longer. Eleven patients are now receiving treatment. Fifteen of the 41 patients whose treatment was completed made an immediate clinical recovery. Of these 15, 6 have had relapses. One patient who suffered a relapse is possibly psychoneurotic, not schizophrenic. In 3 of the other 5 patients with relapses the onset of the disease was recent, with symptoms of less than six months' duration. Of the other 2 patients, 1 had been ill for one and one-half years and the other for approximately two years. Four of the patients who had relapses were women and 2 men. Nine of the 41 patients are still well. Five patients showed marked improvement; 14 recovered sufficiently to leave the hospital; 10 had disease of long standing from which there was little hope of recovery, since, according to Sakel's statistics, all patients with symptoms for more than one and one-half years have a poor prognosis. Some of the patients had been ill for from ten to twelve years and were not expected to show improvement. Of the patients treated 14, or 35 per cent, were greatly improved; 4 were slightly improved but not well enough to leave the hospital, and 17 showed no improvement. One patient alone of those who were not improved formed ideas of persecution concerning the treatment. When the 10 patients with a hopeless prognosis are excluded, the percentage who showed improvement is approximately 45 per cent. The average length of illness before treatment was approximately one and one-half years. The shortest duration of symptoms was approximately three or four months, and the longest, ten or twelve years.

DISCUSSION

DR. WILLIAM L. LONG: Did Dr. Hastings notice whether the prognosis was better in certain types of dementia praecox?

DR. DONALD HASTINGS: Patients with the paranoid form of schizophrenia did best. Those with catatonia did poorly—in fact, according to statistics, in cases in which catatonic symptoms were associated there were no recoveries. The least number of shocks given was eighteen; this patient recovered immediately after a major convulsion and has been well since (February 1937).

DR. FREDERICK H. ALLEN: Were there indications in many cases of previous spontaneous remissions or ups and downs in the condition of the patient prior to the beginning of treatment?

DR. DONALD HASTINGS: A woman aged 30 had been sick periodically for ten years but had not been hospitalized prior to the present attack, during which she had become paranoid. She recovered after the insulin shock therapy, but it is a matter of conjecture whether she would have recovered without special treatment.

DR. WILLIAM L. LONG: I present the history of a patient with dementia praecox who was treated for seven years prior to recent insulin therapy. At the

age of 16, the patient showed the beginning of an adolescent psychosis. For most dips occurring in his weight curve there were adequate explanations; i. e., one in 1935 represented the results of his being placed on a fat-free diet, and one in 1936 followed a fracture of the hip. It was considered a remarkable coincidence that every time the patient had an exacerbation of his psychotic state there was a coincident fall in weight. Improvement followed gain in weight. The same benefit was obtained with insulin treatment, the patient securing about the same degree of improvement from insulin as he did from gain in weight. The insulin treatment was accompanied by a gain in weight and followed by a relapse, which was associated with a loss in weight.

It is postulated that the changes which are brought about by insulin and result in improvement are qualitatively the same as those produced less violently by a gain in weight. It may be that the same metabolic processes are involved in the two kinds of treatment.

DR. B. L. KEYES: With respect to the theory that gain in weight improves the condition of psychiatric patients: Insulin has been used for several years in the treatment of neuroses and psychoses, with considerable success; it is considered especially valuable in fixation of carbohydrates and water in the patient's system, in view of the fact that persons with schizophrenia improve as they gain weight, especially weight put on with exercise and fresh air. During this time, however, physicians were afraid of insulin shock and cut down the dose of insulin whenever the patient showed any evidence of having had too much.

One of the cases reported by Dr. Hastings was that of a young man who had recovered from a psychotic experience a year before the second psychotic episode, which was treated with insulin. During the first psychotic episode he was placed on a farm, where he did light work outdoors, gained from 25 to 30 pounds (11 to 13.5 Kg.) in weight and made thereafter a complete recovery, which held for almost a year. Subsequently, he had a similar, but more severe, psychotic episode. When treated with insulin shock he rapidly gained weight and again made a complete recovery. Both these illnesses were schizophrenic, and it is interesting to speculate how much the gain in weight had to do with the recovery in each instance.

DR. DONALD HASTINGS: When the treatment was first started at the Pennsylvania Hospital, all patients were given diets of 4,500 calories per day, with the result that some gained from 40 to 45 pounds (18 to 20.5 Kg.). All the patients gained weight, but there was no apparent relationship between the increase in weight and the rate of recovery.

DR. L. H. SMITH: About eight or nine years ago, a deeply depressed, manic-depressive patient, of the self-accusatory type, was treated with insulin at the Pennsylvania Hospital, with the hope of producing an increase in weight. She gained some weight, but one day she passed into shock. From the time that she recovered from shock, she showed great improvement. The shock apparently started the trend toward improvement. However, I have seen too many patients gain weight without clinical improvement while sitting around hospital wards to say that the theory has great significance.

DR. FREDERICK H. ALLEN: It might be well to make a distinction between gain in weight and accumulation of fat.

DR. PHILIP ROCHE: In regard to the gain in weight associated with insulin shock therapy: Has there been carried out any study of the water-balance relationships or of the chemical differences in what one may distinguish as "good and bad" fat? It may be important to know not only whether the gain is greater in water or in fat but whether the fat is chemically altered.

DR. D. J. MCCARTHY: In discussing this subject, one must consider whether the chemical change is due to the insulin or the insulin shock or whether it is the result of stimulation or rebalance of the endocrine mechanism.

Since Pitfield (*New York M. J.* **118**:217, 1923) reported on the use of insulin to increase weight in children, I have been using insulin in small doses to effect the same result in the psychoses of adolescence. The dose varied from 5 to 20 units per day, with usually a gain in weight of from 10 to 40 pounds (4.5 to 18 Kg.). I have already reported on the large percentage of recoveries in this group of cases. The effect of the insulin was twofold: (*a*) stimulation of the secondary endocrine function, and (*b*) fixation of the carbohydrates. Treatment in these cases varied from four to six months.

Much has been said in this discussion with reference to the negligible factor in increase in weight. It should be understood, however, that there is a great difference between a gain in weight in patients with chronic conditions and the purposeful gain in weight produced rapidly by a constructive system of therapy. In the first case all the factors that make for the disturbance in the chemical functions of the body leading to the mental disorder are neglected and, without constructive treatment, may even become accentuated. It is as if one treated a patient with tuberculosis merely by having him put on fat in an overheated and vitiated atmosphere.

This is in marked contrast to treatment based on a definite theory as to the production of the disease. I assume that when a brain that has acted normally for twenty or thirty years shows complete or violent dysfunction in the course of a month or so, there must be either a definite change in the nutrition of the brain or damage to the brain cells by violent or definite toxemia. In either event, there is definite alteration in the nutritional blood supply to the brain.

The chemical activity of the body up to the time of puberty and adolescence is concerned with growth. When full growth is obtained there is a rapid change in the mechanism, and the chemical function for the next twenty years is concerned with reproduction. After this period another change is concerned with involution.

The first change is intimately concerned with sex and the sex organs and is mainly endocrine—a pituitary, thyroid, parathyroid, adrenal, gonadal and possibly pancreatic mechanism.

I assume that when there is in early childhood an intense, chronic infection, such as tuberculosis, focal infection, influenza, pertussis or syphilis, there is an intensive strain on the defensive endocrine system for three or four years, or longer. In tuberculosis there is evidence of injury to the thyroid, adrenals, and other glands. The child recovers from this early infection but is left with damage to the endocrine defensive mechanism and grows up with marked arterial hypotension, visceroptosis, flatfoot, etc.

When the change from growth to the reproductive phase takes place at adolescence, the strain on the endocrine system is so great that the already damaged endocrine organs are not able to meet the sudden demand. The pathologic change, not only in the endocrine but in the other vital organs, results in the forms of cerebral intoxication that I have called adolescent psychoses, irrespective of their classification. If at this period focal infections in the teeth, sinuses, tonsils, gallbladder or appendix obtain, all these factors are accentuated.

With this hypothesis as a working basis, during the gain of weight resulting from the use of insulin, an attempt is made to put the body in physiologic balance. All the focal infections are removed, and an effort is made to secure full functional action of the liver, pancreas, kidneys and cardiovascular system.

A gain in weight of 20 or 30 pounds (9 or 13.5 Kg.) under these conditions, with the patient under the full Weir Mitchell rest regimen, carried out in fresh air, as in tuberculosis, will, in my experience, give as satisfactory a percentage of good results in the adolescent psychoses as the more violent insulin treatment under discussion. Insulin can, of course, be used in a dose much larger than I used originally—from 15 to 50 units—short of production of shock.

The more violent insulin treatment would have its value in cases in which the disease does not yield to the more conservative treatment.

I prefer to try the more conservative treatment for three or four months rather than risk the dangers of the more radical method. I should not, however, procrastinate longer than four months, if prospective good results were not in sight.

DR. B. L. KEYES: In discussion of insulin shock treatment, one factor requires serious cognizance. Neuropathologists say that after death due to hypoglycemia extravasations of blood are observed in the region of the basal ganglia and between the fibers and that the picture somewhat resembles that of postencephalitic parkinsonism. I have wondered about the possibility of development of a postencephalitic syndrome several years after insulin shock treatment. It is necessary to keep such a danger in mind so that one may modify the nature of the treatment as one learns to use it better. When malaria was first used in treatment for dementia paralytica, one demanded a great many chills and high temperatures; now it is known that as good results can be secured with greatly modified methods of hyperpyrexia. It is to be hoped that more will be learned of the effective handling of insulin and of the development of more accurate methods of recognizing degrees of shock and when termination of the shock should take place.

RÉSUMÉ OF RESULTS WITH INSULIN SHOCK THERAPY AT THE PHILADELPHIA GENERAL HOSPITAL. DR. HERBERT FREED.

It is difficult to date correctly the beginning of a psychosis. Usually the onset is dated from the first frank evidence of abnormal behavior. This probably is antedated by various periods of psychotic thinking and abnormal behavior that are still socially acceptable to the patient's family, if not to his friends. However, this task is simple as compared with judging the degree of improvement a patient exhibits after treatment. There constantly rises the question: Where does the prepsychotic personality cease and the manifestation of psychosis begin? Furthermore, a depressed, hypochondriacal youth, with a condition diagnosed as schizophrenia, may respond to insulin therapy with hypomania of such a degree that the family considers him better than he ever was. Was the psychiatrist wrong in his original diagnosis, or can one change for indefinite periods the personality of a person by insulin treatment? The few statistics now presented must be considered in this light.

In 29, or 70 per cent, of 41 cases of schizoprenia at the Philadelphia General Hospital in which treatment has been finished, sufficient improvement has been shown to permit discharge. However, some of the patients, perhaps up to 20 per cent, might have remained if they had been in a state institution, where the enthusiasm for testing the possible benefits of a new treatment may not have run away with better judgment. Some of the patients undoubtedly would have improved spontaneously. It must be noted that of the 70 per cent in which improvement was shown, 16, or 55 per cent, were classified as cases of complete remission, and 7, as cases of incomplete remission with improvement which in a few instances was progressive even after discharge, so that the remission can now be classed as complete. However, reclassification was not made at this time. In 12 cases, or 26 per cent the result was classified as complete failure, since sufficient improvement was not shown to permit the patient to leave the hospital. In the majority, 76 per cent of cases in which there was improvement, the disease had been of short duration, that is, six months or less. The longest duration of psychosis was five years, with a partial remission after treatment. In 59 per cent of cases in which there was no improvement, the disease had lasted also six months or less.

Practically all the complications of insulin shock therapy listed by various observers have been encountered. They include: pulmonary edema; convulsions; prolonged nonhypoglycemic coma; after-shock; subarachnoid hemorrhage; pulmonary infection, probably abscess of the lung of nonspecific origin; infection of the arm following a perivenous injection; dislocation of the jaw; hemiparesis of three days' duration; aphasias of varied types; amnesia, and, finally, circulatory failure with death (in 1 case). The last case will be described in greater detail, in order to counteract the impression that one may obtain from reading the circular-

ized letter by Dr. Stanley Cobb (*New England J. Med.* **217**:195 [July 29] 1937). My colleagues and I are cited in this letter to the effect that we would report on the brains of 5 patients who died of hypoglycemia, as well as the case of subarachnoid hemorrhage. I wish to emphasize that these brains were from patients who died of spontaneous hypoglycemia, not of induced insulin shock. Furthermore, I wish also to point out that the patient with subarachnoid hemorrhage made an apparently complete recovery from both the hemorrhage and the psychosis.

In the case of circulatory failure with death, the following are the details: A white woman aged 35 was intensely depressed and suicidal. She required restraint from the time of admission until death. Though she had once weighed about 160 pounds (72 Kg.), she weighed at the time of admission only 85 pounds (38.5 Kg.), because of refusal to eat. She had been critically ill for weeks. Thirty-two units of insulin in divided doses was given to stimulate appetite, but she continually refused to eat and required tube feeding; with the consent of her husband, 60 units of insulin in one dose was tried. The patient passed into shock but refused to eat. Since she was so uncooperative that a nasal tube could not be passed, the treatment was terminated by the intravenous administration of dextrose. On the following day 4 doses of insulin of 20 units each were given during the course of an hour. At the end of the treatment the patient passed into coma; after coma lasting one hour and a quarter, she was fed with a tube, but did not respond satisfactorily; within the next hour about 100 Gm. of dextrose was given intravenously. The patient passed into a state of circulatory collapse and died despite stimulation within six hours. The brain has not yet been studied completely.

Finally, I should like to have two important points discussed: 1. Duration of the individual period of coma. Vienna workers recently decided two hours of deep coma should be the maximum length of treatment. However, it is known that certain therapeutists allow some patients, particularly those of the paranoid group, to have three or four hours of coma.

2. Duration of the course of treatment. When should one decide that the patient will not be benefited by insulin treatment and terminate the course of therapy? Fifty treatments has been suggested as the proper course. I heard recently of a patient in a New York hospital who did not improve until he had had eighty treatments.

DR. W. L. LONG: Do you think convulsions are necessary in the production of cure?

DR. HERBERT FREED: It is my impression that about 50 per cent of the patients improve after convulsions. I have seen a few patients who showed marked improvement after a convulsion. One patient had thirty or forty treatments of insulin without marked improvement; then she had a severe convulsion one hour after the injection of insulin, and her symptoms disappeared completely. She rested for a week, only to have a relapse. She was given treatment for a few more weeks and again improved, but not as completely as before. A certain test was made, and immediately thereafter she had a relapse. A few more weeks of treatment did not give any therapeutic response. After an interval of a few months without treatment or improvement convulsive therapy with camphor in oil was begun. A slight degree of improvement was noted. The treatment had to be interrupted when she was transferred to a state institution. When I last heard about her, she had not shown further improvement.

DR. PHILIP ROCHE: What determinations, if any, were made of the levels of the blood sugar during the maximum depth of shock?

DR. HERBERT FREED: The lowest blood sugar level was 9 mg. Work has been done in the Galveston State Psychopathic Hospital to show that patients tend to pass into coma when the level of the spinal fluid sugar drops to between 15 and 30 mg., although it seems to be independent of that of the blood sugar. It is interesting that Sakel and Dussik, in a report on the treatment of 104 patients, mention that it has been known for some time that, whereas in normal persons

the amount of sugar in the spinal fluid lies between 50 and 70 mg., in psychotic patients there are often distinct variations from the normal.

DR. DONALD HASTINGS: As to the blood sugar levels obtained during maximum depth of shock: There is apparently no relation between shock and level of the blood sugar. I doubt whether one can say that when the blood sugar approaches a certain level there is shock. For example with a dose of 40 units the patient may show only a heavy sweat; yet the blood sugar may be as low as it is two weeks later, when he is in coma. Some blood sugar levels have been recorded as 0. There is a great deal of individual variation.

DR. JOSE ZOZAYA, Gladwyne, Pa.: In studying the blood sugar after large doses of insulin, one often finds the lowest level within one-half hour. In about two and one-half hours the patient becomes comatose. I think that during the two and one-half hours, when the blood sugar level has reached its lowest point, glycogen is being utilized.

DR. L. H. SMITH: A moving picture in color taken in the psychopathic wards of the Philadelphia General Hospital demonstrates the technic of insulin therapy and the accompanying clinical responses.

CLINICAL EXPERIENCES AND RESEARCH IN THE TREATMENT OF SCHIZOPHRENIA WITH INSULIN AT GLADWYNE COLONY, GLADWYNE, PA. DR. JOSE ZOZAYA, Gladwyne, Pa.

Thirteen patients have been treated.

Results.—Three patients were apparently cured. One, a man, had been ill for one year; treatment lasted for five weeks. The second, a woman, had been ill for two and one-half years and was under treatment for six weeks. The third had been ill for seven months, with a relapse; there had been a previous relapse five years before. Treatment was continued for eight weeks.

Four patients were improved. One had been ill for two years, with a relapse for three months. Treatment lasted eight weeks. The second had been ill for five months and was treated for three weeks; treatment was stopped because of a marked idiosyncrasy for insulin. The third had been ill for two and one-half years and was under treatment for seven weeks. The fourth had been ill for two years and was treated for three weeks; treatment was stopped because of marked cardiac reactions.

The other 6 patients showed no definite improvement. The duration of illness ranged from two to ten years. Treatment was continued for from two to seven months.

Convulsions.—Five of the patients treated had convulsions during shock or coma.

Accidents.—Difficulties in respiration from transient edema of the glottis occurred in 1 case. In 1 case there was swelling of the tongue and glands of the neck, and in 1, pulmonary edema with a convulsion. There were no deaths.

Dosage.—The dose necessary to produce deep coma ranged from 40 to 185 units.

Duration of Coma.—The usual duration of coma allowed was from one to two and one-half hours, depending on the condition of the patient.

Termination.—Coma was terminated usually by the administration of a 33 per cent solution of dextrose intravenously, with the addition at times of tea containing 50 Gm. of sugar by nasal tube.

In an approach to a study of the changes that occur during treatment with insulin shock, my colleagues and I followed our previous methods of studying the physicochemical changes in the blood serum. The specimens studied were taken (1) while fasting, before insulin was given; (2) during and just before the termination of coma; (3) at the time of termination, fifteen or twenty minutes after the injection of dextrose, and (4) two hours after termination. With each specimen,

measurements were made of: the specific gravity, viscosity, blood sugar, blood cholesterol, total protein of the serum, albumin, pseudoglobulin and euglobulin fractions, cell volume (hematocrit readings) and osmotic pressure at 0 C., to insure chemical stability of the serum. The average values for these measurements are given in the accompanying tabulation.

	Fasting	Coma	Termination	Two Hours After Termination
Specific gravity	1.0265	1.0275	1.0275	1.0270
Viscosity	1.725	1.723	1.727	1.726
Total protein, per cent	7.17	7.46	7.53	7.49
Albumin, per cent	4.64	4.77	4.61	4.78
Pseudoglobulin, per cent	1.17	1.30	1.23	1.29
Euglobulin, per cent	1.34	1.34	1.71	1.64
Albumin/globulins	1.86	1.81	1.57	1.64
Dextrose per 100 cc.	100 mg.	21 mg.	64 mg.	77 mg.
Cell volume (hematocrit reading)	35.19	35.44	35.43	34.40
Cholesterol per 100 cc. blood	200 mg.	215 mg.	224 mg.	215 mg.
Osmotic pressure, mm. of mercury	12.37	12.23	12.00	10.99
Osmotic pressure per gram of protein	1.74	1.73	1.63	1.62

From an analysis of these data, the following suggestions are made: The changes in specific gravity and the total protein of the blood serum from the time of fasting up to two hours after termination of shock, with the highest change immediately after termination, suggest concentration of the blood, probably by loss of water. The variations in the cell volume, being small, do not show changes in the same direction, leading one to believe that the changes in water content are due to the marked amount of water lost through perspiration during the treatment and do not affect the blood volume; mainly, they drain the intercellular spaces. No doubt there also occur changes in the physicochemical nature of "bound water" in the proteins.

The increase in the euglobulin fraction after termination of shock is the outstanding and most frequent finding; this change occurs immediately after the intravenous injection of dextrose, after the patient has been depleted of sugar storage by the continuous action of insulin. The explanation of this finding is not clear, but in view of our previous studies on serum proteins in different pathologic conditions we believe that an increase in the euglobulin fraction shows a definite "reaction" in the immunologic sense, suggesting stimulation of the tissue (reticulo-endothelial system) that has to do with immune reactions.

While there is a small increase in cholesterol at the time of termination of shock, this increase is not significant. The osmotic pressure of the serum shows a marked fall per gram of protein after termination of coma; it is constant during coma and lower two hours after termination. From theoretical calculations we believe that this change is due principally to protein hydration, which diminishes the number of molecules per volume, increasing the distance between each molecule.

In conclusion, we believe that insulin shock and its sudden termination by dextrose markedly stimulate the "reactive mechanisms of the body," bringing about fundamental changes in the physicochemical behavior of the serum proteins, which in turn affect the physiologic equilibrium of the body cells, especially in respect to the interchange of water.

PATHOLOGIC CHANGES IN THE NERVOUS SYSTEM INCIDENT TO ALTERATIONS IN THE PHYSIOLOGIC DYNAMIC EQUILIBRIUM OF THE BLOOD (INSULIN SHOCK). DRS. HELENA E. RIGGS and J. O. GRIFFITHS.

Injection of large doses of insulin in nondiabetic persons produces not only hypoglycemia but alteration of the physiologic dynamic equilibrium of the blood. This alteration is not specific for insulin but occurs also in association with diabetic acidosis, surgical shock, hemorrhage, ether narcosis, carbon monoxide poisoning and deficiency states. The cerebral stasis thus induced stimulates the sympathoadrenal mechanism, in an attempt to restore homeostasis.

However, damage to the cerebral vascular bed during the period of acute stasis may institute a vicious cycle, leading to degenerative changes in the viscera, the peripheral vascular system and the nervous system.

DR. E. D. BOND: It has been interesting to note the difference in the results obtained in two hospitals in which experts are giving insulin treatments. Reports from the Worcester State Hospital are disappointing. At the Harlem Hospital, New York, the results are encouraging. The person who pointed this out wondered whether the effort at the Worcester State Hospital to find out why the patient recovered has interfered with the results of treatment. At the Harlem Hospital the only object is to secure favorable results. It is interesting to note that the Philadelphia General Hospital has now treated 41 patients—the same number that my colleagues and I have treated at the Pennsylvania Hospital. They record 16 patients as recovered while we have recorded 15. In some cases there has been relapse to a greater or less extent. Does this mean that psychiatrists are sending out some recovered patients into conditions which are too much for them? Perhaps they have done that which cannot be done in cases of healed lesions of tuberculosis. They have checked the active process and then discharged the patients without instructions as to what to do in the future. Certainly, more time will be needed to evaluate insulin shock therapy. In facing the possibility that hemorrhages are produced in the brain, which may later cause trouble, one must balance this against the inevitable results if the patients are not given insulin shock. Will the deterioration be worse in the one way or in the other?

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding*

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SYNCOPE, CONVULSIONS AND THE UNCONSCIOUS STATE: RELATIONSHIP TO THE HYPERACTIVE CAROTID SINUS REFLEX IN 1,000 PATIENTS IN AN INSTITUTION FOR EPILEPSY. DR. LEON J. ROBINSON, Palmer, Mass.

The importance of the hyperactive carotid sinus reflex in the causation of syncope has lately been receiving deserved emphasis. The carotid sinus is the bulbous dilatation at the bifurcation of the common carotid artery. In patients who possess a hypersensitive carotid sinus, stimulation of the sinus by pressure will often induce syncope or convulsions.

Specialized receptors are present in the adventitial layer of the carotid sinus. From these receptors afferent impulses reach the medulla by way of the intercarotid, glossopharyngeal, vagus and hypoglossal nerves and the cervical portion of the sympathetic cord. Normally, the arterial blood pressure maintains a relatively constant level within the sinus. The receptors of the sinus may be stimulated by sudden changes in arterial pressure or by external pressure on the wall of the sinus. These sensory stimuli, passing contralaterally in the brain stem, travel over a variable efferent pathway, which Weiss and his colleagues have ably classified (Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex: Diagnosis and Treatment, Arch. Int. Med. **58**:4007 [Sept.] 1936). They present three dominant effects: (1) the vagal type, with the efferent response traveling over the vagus nerve to produce sino-auricular or auriculoventricular block with resultant asystole and syncope; (2) the depressor type, the afferent arc of which passing by way of the aortic depressor nerves accounts for vasodilatation and marked drop in blood pressure unassociated with bradycardia or arrhythmia, and (3) the cerebral type, in which syncope occurs without cardiovascular changes.

An increase in pressure within the carotid sinus will produce reflexly hypotension and bradycardia. Converse effects follow decrease in pressure. Normally, the sinus, like the aortic, depressor reflex, guards against sudden excessive increases in intra-arterial pressure. In patients with an abnormally sensitive carotid sinus reflex, exaggerated depressor effects, often accompanied by syncope, result from slight increases in intrasinus pressure.

The vagal type of sinus syncope can be abolished by atropine, which paralyzes the endings of the vagus nerve, or by epinephrine, which stimulates the ventricles to assume an independent rhythm sufficiently rapid to offset the symptoms despite the heart block. The depressor type of attack cannot be prevented by atropine but can be prevented by epinephrine, which constricts the small blood vessels and thus abolishes vasodilatation. The cerebral type of sinus syncope is impervious to atropine or epinephrine. Infiltration of the carotid sinus with procaine hydrochloride prevents syncope of any of these types by anesthetizing the sinus receptors. Likewise, surgical denervation of the carotid sinus abolishes the abnormal response in all types.

With these facts in mind, a study was undertaken to determine what percentage of patients in an institution for epileptic patients might exhibit a hypersensitive carotid sinus reflex and to determine whether this, when present, was the sole cause of seizures or whether it was an additional factor present in some patients who had attacks of unconsciousness from other causes.

A series of 1,000 patients was examined, comprising cooperative institutional patients in the wards of the Monson State Hospital for epileptic patients, as well as outpatient visitors. In every instance syncope, convulsions or transitory loss of consciousness brought the patient to the hospital. In case of the ward patients who exhibited a hyperactive carotid sinus mechanism, there were adequate causes (aside from syncope) for institutionalization, such as mental deficiency and periods of dementia or mania.

With the patient standing, firm pressure for one minute was exerted with the tips of the fingers over the carotid artery from the cricoid cartilage to the angle of the jaw. Only one side was stimulated at a time, to avoid cardiac standstill. The blood pressure and pulse rate were determined during maintenance of the carotid sinus pressure.

Nine of the 1,000 patients tested were found to possess the carotid sinus syndrome; that is, 0.9 per cent of the patients exhibited the effects of a hyperirritable carotid sinus mechanism. The ages of the patients ranged from 4 to 82 years. There were 8 males and 1 female.

The following case illustrates the type of material.

A. B., a man aged 24, with no arteriosclerosis, had had seizures since 17 years of age. The basal blood pressure was 110 systolic and 70 diastolic, and the pulse rate 70. The diagnosis was epilepsy, of unknown cause, and mental deficiency (imbecility, with an intelligence quotient of 45). There was an average of six spontaneous generalized convulsions a month. During the seizure there was loss of consciousness, generalized clonic movements of all extremities and falling to the ground. The attack ceased within half a minute. There was no postconvulsive confusion.

In an induced seizure pressure on the right carotid sinus maintained for ten seconds caused weakness and slowing of the pulse rate from 70 to 22 a minute, hyperpnea, decrease in blood pressure from 110 systolic and 70 diastolic to 80 systolic and 60 diastolic, generalized clonic convulsion and slumping to the floor. The attack ceased six seconds after pressure on the sinus was released. The sensorium was clear immediately after cessation of the convulsion. Only after recovery did the patient realize that an unusual event had occurred. Pressure on the left sinus produced a similar response. On recovery $\frac{1}{60}$ grain (1.1 mg.) of atropine sulfate was given intravenously. Three and six minutes after the administration of atropine, the blood pressure was 110 systolic and 68 diastolic, and the pulse rate, 74. There was no pupillary dilatation or dryness; the carotid sinus was still hypersensitive on stimulation by pressure. After a short interval,

throughout which hypersensitivity of the sinus was demonstrable, 0.5 cc. of epinephrine hydrochloride was given subcutaneously. Two minutes later pressure on the right sinus produced only hyperpnea and mild, ill sustained clonic movements of the left arm. Thirteen minutes after the administration of epinephrine, pressure on the carotid sinus maintained for one hundred and twenty seconds caused only hyperpnea. There was no effect on the heart rate, which persisted at 84, or on the blood pressure, which registered 100 systolic and 75 diastolic. This was in marked contrast to the effects of the initial pressure on the sinus, which was maintained for only ten seconds. At frequent intervals pressure was made on the sinus, but not until four hours and thirteen minutes after the administration of epinephrine did the effects of the hypersensitive carotid sinus return.

This case exemplifies the vagal and depressor types of carotid sinus syncope, characterized by cardiac slowing and a drop in blood pressure. Characteristically, too, epinephrine was efficacious in preventing the induction of syncope by pressure over the hyperactive carotid sinus.

In 3 additional cases the sinus response fell into the category of the vagal and depressor types. In 2 cases in this series, the response conformed to the cerebral type.

In the 3 remaining cases a combination of vagal, depressor and cerebral responses was presented, for while a decrease in the cardiac rate and blood pressure was exhibited, there was no response to epinephrine.

The fact that spontaneous and induced seizures are alike is strongly in favor of the assumption that the carotid sinus syndrome is responsible for all seizures in a given case.

Vertigo, tinnitus, weakness, epigastric distress, hyperpnea, numbness or tingling of the extremities or anxiety, or any combination of these, may herald syncope either of sinus or nonsinus origin. In sinus syncope the aura directly precedes the attack. However, the short interval between the premonition and the seizure is also a common occurrence in nonsinus syncopal conditions, such as orthostatic hypotension, hyperinsulinism and "epileptic" seizures. When premonitory manifestations consist of hyperpnea, dysphagia or hoarseness, sinus syncope should be borne in mind.

Sinus syncope nearly always occurs when the patient is in the vertical position. This is a relative, rather than an absolute, criterion in favor of the diagnosis of sinus syncope, as seizures due to other mechanisms may, and do, overtake persons while in the vertical position. Furthermore, patients with a hyperirritable carotid sinus, even while in the horizontal position, may exhibit convulsions and loss of consciousness on premeditated or accidental stimulation of the carotid sinus.

Spontaneous sinus syncope may be produced by patients through unintentional pressure on the hyperirritable carotid sinus, in the form of sudden movement of the head and neck, constricting neckwear or swallowing effervescent liquids.

In patients with a hypersensitive carotid sinus reflex, syncope can be reproduced on many, and usually all, occasions by digital pressure over the hyperirritable carotid sinus. The suddenness and intensity with which pressure is made over the sinus are often decisive factors in the production of spontaneous as well as induced seizures. Gradual or light pressure frequently proves ineffective. Furthermore, if this mechanical stimulation is discontinued with the appearance of mild signs, complete syncope may not follow.

Even in patients known to possess the sinus syndrome, pressure over the sinus may at times be ineffective in demonstrating the phenomenon.

The duration of the unconscious state is generally short (from a few seconds to several minutes) in carotid sinus attacks, as the horizontal position, into which the patient falls, usually ends the syncope. Exceptions to this generalization occur, as in one of our cases.

Carotid sinus syncope is often characterized by a sudden fall with, or more rarely without, convulsive movements. The latter are clonic and, as a rule, generalized. However, with close observation we noted that induced carotid sinus convulsions began with clonus in the arm and leg contralateral to the sinus stimu-

lated. Even when paresthesia is manifest, it is usually present in the contralateral arm. Urinary or fecal incontinence during sinus seizures may simulate epileptic convulsions.

After sinus syncope the sensorium, as a rule, clears with remarkable rapidity. Moreover, postsyncopal confusion is apt to be absent, and even headache, vertigo or lassitude is rare. When sinus syncope is prolonged these features are, on the contrary, common.

Spontaneous sinus attacks may recur frequently (within a few hours or days) or relatively infrequently (months or years apart), so that this feature does not aid the diagnosis in any characteristic way.

The oral administration of from ¾ to 1½ grains [48.6 to 97.2 mg.] of phenobarbital or its withdrawal did not seem to alter the incidence of sinus seizures, either spontaneous or induced. Soluble phenobarbital U. S. P. (sodium phenobarbital), 5 grains (0.324 Gm.), was given intravenously in one case without lessening the ease or character of production of induced sinus syncope during a period of two and a half hours, despite marked somnolence.

An attempt was made to establish a therapeutic criterion. The ideal therapeutic test for distinguishing carotid sinus syncope from other types of syncopal attacks would be some form of therapy which could specifically prevent sinus syncope, but not other types. Except for surgical extirpation of the carotid sinus, this requirement is not at present completely fulfilled. However, it has been demonstrated by Weiss and his colleagues (in the article previously cited) that atropine prevents the vagal type of sinus syncope and that epinephrine prevents both the vagal and the depressor type.

Our cases included none in which there were pure vagal effects, but in 5 of the cases in which depressor effects were evident epinephrine was effective in preventing induction of sinus syncope. The disadvantage of epinephrine for continuous use was the necessity for hypodermic injection. Therefore, as suggested by Weiss and his co-workers in the article cited, ephedrine sulfate was used orally. Even when induced attacks were aborted its effectiveness disappeared in from one-half to one hour after administration of a dose of 1 grain (64.8 mg.) by mouth. For ephedrine we therefore substituted the similar sympathomimetic drug benzedrine sulfate.

Benzedrine sulfate in varying doses was given to 4 of the patients exhibiting the depressor response on stimulation of the sinus. At intervals after the administration, attempts were made to elicit sinus syncope. The initial dose of benzedrine sulfate was 10 mg., and if this dose proved ineffective in preventing induction of a sinus attack the amount was increased 10 mg. at a time. From 20 to 30 mg. proved effective on many occasions in preventing the induction of sinus syncope, but as much as 50 mg. in a single dose was at times necessary.

The efficacy of benzedrine sulfate was demonstrable as early as twenty-five minutes after oral administration of 10 mg., but the hyperirritability of the sinus returned eighty minutes after the dose of 10 mg. Often, however, when 20 or 30 mg. was given, syncope could not be induced for as long as from three and one-half to four hours.

The 4 patients selected were then given the amount of benzedrine sulfate which had previously been determined as adequate to prevent induction of sinus syncope. As the length of time this dosage could be expected to be effective had also been determined, the medication was repeated at intervals slightly shorter than the length of time necessary for the effect of medication to wear off. The dose varied from 20 to 40 mg. of benzedrine sulfate given three or four times daily.

In the first 3 cases both spontaneous and induced seizures were absent during the period over which the effectiveness of benzedrine sulfate had been demonstrated. In 1 case, although induction of seizures was prevented by benzedrine, spontaneous seizures continued to occur occasionally.

As a control, a series of patients with recurrent convulsions, diagnosed as epileptic in origin, none of whom possessed a hyperirritable carotid sinus were also placed under benzedrine therapy. This group in no case showed improvement

with benzedrine therapy; in a few instances seizures when benzedrine was being administered were more frequent than when placebos of lactose were used.

In the cerebral type of sinus syncope benzedrine does not serve as a therapeutic test, as this type is not amenable to drug therapy.

In the light of the criteria discussed, it is generally possible to determine whether a hyperirritable carotid sinus is the mechanism involved in patients complaining of periodic loss of consciousness, convulsions or syncope. Moreover, a patient may have convulsions and syncope due to both a hypersensitive carotid sinus reflex mechanism and a mechanism independent of the carotid sinus reflex.

In 5 patients in this series a hyperirritable carotid sinus reflex seemed to be the sole mechanism underlying all seizures, both spontaneous and induced; in 3 patients there were a hyperirritable carotid sinus reflex and an additional cause of convulsions. As the last patient with a hyperirritable carotid sinus died of an intercurrent infection before a comprehensive study could be completed, it is impossible to state whether or not the sinus syndrome was the sole cause of all seizures.

Of those in whom the abnormal sinus reflex seemed to be the sole mechanism underlying convulsions, only 1 patient did not respond to medicinal therapy. Despite the fact that in his case syncope can be provoked by sinus pressure, the man has not had a spontaneous seizure for years and hence requires no therapy.

The note of caution sounded by Ask-Upmark (*Acta psychiat. et neurol. supp.* **6**:1, 1935) may be sounded again. This is to the effect that indiscriminate extirpation of the carotid sinus, when performed without critical rationale for the purpose of abolishing epileptic seizures, is open to censure, as well as to disappointment.

PRACTICAL ASPECTS OF CHILD GUIDANCE: A CRITICAL ANALYSIS OF 500 CASES IN THE CHILD GUIDANCE CLINIC OF THE SPRINGFIELD HOSPITAL. DR. CALVERT STEIN, Palmer, Mass.

The problems, with the etiologic factors, findings, diagnoses and treatment, and the results of nearly six years of personal study of 295 boys and 205 girls at the child guidance clinic in Springfield, Mass., are reported in statistical detail. Forty-seven per cent of the children presented problems of habit training, while emotional insecurity was a factor in fully 70 per cent; for 27 per cent there were problems of education and retardation. Most of the children presented more than one problem.

The sixteen sources of reference included health and social agencies, parents, schools, other clinics and physicians. The number of children referred by physicians has risen from 2, in 1933 to 18, in 1936 (this may be compared with 162 children, or 32.4 per cent, referred by the child guidance clinic to a local physician or to other clinics).

The diagnosis of a "normal child" appeared as follows: (*a*) physically normal, in 18 cases, or 3.6 per cent; (*b*) emotionally normal, in 4 cases, or 0.8 per cent, and (*c*) intellectually normal (average and superior) in 252 cases, or 50.4 per cent.

Malnuarition, diagnosed for 30 per cent of the children, appeared as an etiologic factor for only 8.5 per cent. Endocrinopathies were diagnosed for 31 per cent, but were considered to be of etiologic significance in only 8 per cent of the 500 children. Visual defects were diagnosed for 22 per cent, but were found to be an etiologic factor for only 3.5 per cent. Dysarthria was diagnosed for 22 per cent; 27 of these children were stammerers or stutterers. Conversion from left handedness was found in only 1 case—that of a child who also exhibited mirror writing.

Treatment for one half of the children consisted of parental guidance. One third of the children were referred to their own physicians or to other clinics, one fourth for personal guidance and one fifth each for laboratory studies, dental care, tonsillectomy and endocrine therapy. Changes in school curriculum were advised in 15 per cent of the cases.

The distressingly high incidence of broken appointments during the early part of the study was reduced from 27 to 7 per cent by the simple expedient of requir-

ing the parent to appear in person at the time of application for an interview with the social worker, during which the needs, services and limitations of each party were explained to the other.

Results were interpreted as objectively as possible from the reports of parents, teachers, social workers and personal observations. Twenty-seven per cent of the 500 children did not improve, and for 19.2 per cent the results are unknown (treatment of 83 children in the last group is being continued). Of the 404 children for whom the results are known, two thirds are believed to have improved since their contact with the clinic. How much of this improvement belongs to the *post hoc, ergo propter hoc* variety it is, unfortunately, impossible to determine. However, the constantly increasing demands for services at the child guidance clinic and its ever lengthening waiting list seem to indicate that a reasonable share of the credit for such improvement belongs to the science and art of child guidance.

The conclusion is inescapable that since a large part of the work of a child guidance clinic is with the parents, the task could be simplified greatly if the elements of mental hygiene, like those of physical hygiene, were carried into the public schools, especially into the high schools and teachers' colleges; for when more people learn to recognize the importance of emotional insecurity in childhood, prophylaxis should become more universally applied.

PHILADELPHIA NEUROLOGICAL SOCIETY

J. W. McCONNELL, M.D., *President, in the Chair*

Regular Meeting, Oct. 22, 1937

NEW ASPECTS OF NERVOUS DISORDERS IN AVITAMINOSIS.[1] DR. H. M. ZIMMERMAN, New Haven, Conn (by invitation).

An attempt is made to evaluate the role which vitamins play in producing nervous disorders. For preservation of the health of the human nervous system a diet containing both vitamin B_1 and vitamin B_2 is essential. Absence of the antineuritic vitamin B_1 from the diet is responsible for lesions of peripheral nerves in both dog and man. These lesions consist of noninflammatory, degenerative changes in the medullary sheaths and, subsequently, in the axis-cylinders. This form of nerve involvement is illustrated with clinical and anatomic case records.

Absence of vitamin B_2 from the diet is responsible for similar lesions in peripheral nerves. In addition B_2 avitaminosis is associated with degeneration of the posterior columns in experimental animals as well as in man, and the lateral spinal tracts are occasionally involved. In man certain ganglion cells of the brain and spinal cord show alterations of the "axonal" type. Case histories are presented to illustrate this type of avitaminosis.

VITAMIN B DEFICIENCY IN CLINICAL MEDICINE. DR. KATHARINE O'SHEA ELSOM, Ardmore, Pa. (by invitation).

From experimental study of clinical vitamin B deficiency conducted at the Hospital of the University of Pennsylvania during the past five years, my associates and I have concluded that the manifestations of early deficiency form a characteristic syndrome the signs of which are referable chiefly to the gastro-intestinal tract and the nervous, cardiovascular and hematopoietic systems. The symptoms most frequently encountered were: sore tongue, anorexia, epigastric distress, abdominal

1. In this paper and in the accompanying papers, the term vitamin B includes all factors of the vitamin B complex; individual members are referred to as B_1 and B_2 (G).

discomfort, accompanied either by constipation or intermittent diarrhea; pains and paresthesias located chiefly in the lower extremities, dyspnea on slight exertion, and easy fatigue. The most characteristic alterations in physical signs were: loss of weight; disappearance of papillae of the tongue, followed in some instances by ulcers of the margins and reddening, impairment and often temporary loss of vibratory sensation; edema; tachycardia, and, on special examination of pregnant women taking a diet deficient only in vitamin B, a macrocytic type of anemia. There is no experimental evidence to suggest that in human beings manifestations of deficiency referable to one system occur without characteristic evidence of involvement of the other systems, and it is therefore considered unwise to attribute to vitamin B deficiency clinical phenomena which are not accompanied by other characteristic evidences of the deficiency.

In the absence of satisfactory clinical tests, the diagnosis of vitamin B deficiency must be made chiefly from knowledge of the characteristic clinical picture and of the factors which alter the requirements for vitamin B and so predispose to the development of deficiency. The clinical conditions which are accompanied by an increased requirement for vitamin B are those associated with an increase either in body weight or in total metabolism, the vitamin B requirement being directly proportional to these two factors. The chief clinical conditions which result in an increased requirement for vitamin B and which, therefore, are most likely to be associated with signs of deficiency are: abnormal gain in weight, as in pregnancy; excessive total caloric intake; prolonged fever, and hyperthyroidism.

In treatment of manifest deficiency or in fortification of the diet to prevent such deficiency, the optimum intake of vitamin B, as deduced from animal experiments, is probably approximately five times that necessary to prevent deficiency for the average adult; this therapeutic dose amounts to about 5,000 Sherman units. From experimental evidence it is apparent that human beings require all fractions of the vitamin B complex; in view of this fact, it is unlikely that purified fractions of the B complex will completely relieve vitamin B deficiency as it is encountered in clinical medicine.

Neurologic Aspects of B Avitaminosis. Dr. F. H. Lewy.

Determination of the strength duration curve for nerve irritability permits one to demonstrate numerically changes in nerve function long before symptoms or clinical signs of a nerve lesion appear. By this method, changes in nerve irritability have been discovered in a number of metabolic, toxic, infectious, blood and constitutional diseases. The chronaximetric deviation in these diseases is usually accompanied by a characteristic clinical syndrome.

It has been concluded as the result of therapeutic experiments that B avitaminosis is instrumental in producing many parenchymatous neuropathies. The experience that nervous symptoms appear more often in partial deficiency than in complete lack of vitamin B and that vitamin B cannot be stored in an appreciable amount in the body may explain the recent observation that vitamin B deficiency is not such a rare event as was believed formerly. The course of vitamin depletion of the tissues makes intelligible why B avitaminosis appears late in diseases. It is not the acute but the chronic stage of an intoxication or infection which elicits signs of nerve involvement.

Loss of appetite and digestive power as consequence and as cause of vitamin B deficiency form a vicious circle, which is best seen in pernicious anemia. Since vitamin B has an influence on the carbohydrate metabolism, it plays a role in diabetes and its polyneuropathy. Some observations suggest that the changes in the central nervous system following intoxications and infections, both sclerosis of tracts and involvement of the basal ganglia and cortex, have a relation to vitamin B deficiency.

The clinical syndrome, electrical examination of the peripheral nerves, determination of the pyruvic acid content of the blood and urine, blood picture and analysis of the gastric contents offer opportunity for an early and reliable diagnosis of vitamin B deficiency.

DISCUSSION

DR. JAMES H. JONES (by invitation): Concerning the fundamental changes within the body that may cause these pictures of vitamin B deficiency, practically nothing is known, with the possible exception of vitamin B_1. For knowledge of this phase of the subject one must depend largely on the work of Peters and his associates, in England. They have taken brain tissue from pigeons with avitaminosis, ground up the tissues and studied the oxygen uptake in a Warburg apparatus. As compared with the normal, they found that the rate of oxygen uptake is considerably reduced in polyneuritic animals. When pure vitamin B_1 was added in vitro the oxygen uptake returned practically to normal. Further studies indicated that there is accumulation of lactic acid in the abnormal tissue, and at first Peters and his co-workers thought that vitamin B_1 had something to do with oxidation of lactic acid. Subsequent work showed that pyruvic acid also accumulates in abnormal amounts and that the increase in lactic acid, instead of having to do with accumulation of lactic acid, is secondary to increase in pyruvic acid.

In a paper which reached this country only last week, Peters and his colleagues carried the research still further; they claimed that vitamin B_1 has something to do with the disappearance of pyruvic acid other than its oxidation. It is associated with metabolism of pyruvic acid, which is an essential part of carbohydrate metabolism. They found that the regions of the brain most affected are the optic lobes and the lower part of the brain. When they injected lactic acid or pyruvic acid into these portions of the brain of animals, they did not produce the effects of vitamin B_1 deficiency. They concluded that this deficiency is due not to a toxic condition but to partial starvation of energy caused by incomplete metabolism of carbohydrates. They expressed the opinion that many symptoms resulting from vitamin B_1 deficiency can be accounted for by failure of normal metabolism within the nerve cells. Acute deficiency can be corrected by the simple addition of vitamin B_1, and they reported that injections of vitamin B_1 into the cranial cavity of pigeons with polyneuritis will cure the condition in an hour.

Dr. Lewy mentioned that there is a difference between the acute and the chronic condition. In the chronic condition recovery is much slower; Peters and his co-workers expressed the belief that in such cases nerve lesions may develop from deficiency of carbohydrate metabolism. Once the lesions occur, recovery is much slower. I do not believe that the nerve cells are the only cells in the body which are so affected—in fact, Sherman and Elvehjem reported that oxidation in kidney tissue from polyneuritic chickens is greatly slowed, and Peters' work with the rat seems to show that other regions within the brain are probably affected. If the conclusion of these authors is correct, a definite chemical compound is necessary for cellular metabolism and normal cellular function. Since nerve tissue is the tissue which is first and most affected and since, in turn, it produces the pathologic changes described, the interests of the chemist, the pathologist and the neurologist are brought close together.

DR. ALFRED GORDON: A point not mentioned by any of the speakers is the relation of avitaminosis to progressive muscular atrophy. Mirato and Suzuki carried out experiments on 10 patients with administration of vitamin C. They did not expect regeneration of muscle fibers, but clinical observation showed satisfactory results with regard to power of affected muscles and muscle metabolism. I wish to ask a question about multiple neuritis. In cases of alcoholism the neuritis had always been considered as due to the poison alcohol. Have the speakers abandoned the theory that avitaminosis is the only cause of polyneuritis associated with addiction to alcohol?

Meiman treated a series of patients suffering from polyneuritis with vitamin B_1. One group had a motor type of polyneuritis; the other, a sensory type. Feeding with vitamin B_1 produced greater results in the sensory type. It is suggested that vitamin B_1 has a greater effect on the centripetal than on the centrifugal pathways.

DR. B. J. ALPERS: I wish to ask Dr. Zimmerman about neuritis associated with vitamin deficiency. 1. In cases of alcoholic neuritis, are any changes produced in the spinal cord over a long period, as observed experimentally or clinically? In some cases of alcoholic neuritis changes are shown in the spinal cord, sometimes marked posterolateral sclerosis. I have been at a loss to explain this. 2. How frequently, experimentally or otherwise, are changes observed in the cranial nerves in cases of alcoholic neuritis? 3. What is the condition which leads to development of Wernicke's encephalitis in some cases of vitamin deficiency and not in others? It would be interesting to know whether anything specific is necessary for the development of Wernicke's encephalitis. Finally, I do not understand the evidence for the theory that diabetic polyneuritis is due to avitaminosis.

DR. S. B. HADDEN: The importance of vitamins in the treatment of certain disorders of the central nervous system has long been recognized; tonight Dr. Zimmerman has ably pointed out their value. Every advance in therapeutics has been associated with a wave of wild optimism. In the early days of recognition of the importance of vitamins, those on the fringe of scientific medicine unfortunately exploited them far beyond their worth.

Dr. Lewy recommended that vitamin therapy should not be used indiscriminately until more is known of the specific effect of each fraction of vitamin B. It will require at least twenty years, I believe, before various fractions can be isolated and evaluated by experimental and clinical means. I do not think that one should refrain from vitamin therapy merely because the exact effect of each fraction is not known. It can be said that physicians in general have paid little attention to the matter of diet in disease, and it is unfortunate that such faddists as Hays and others have been able to exist because of lack of emphasis on dietary measures.

Those who have worked in the Philadelphia General Hospital readily appreciate that the therapeutic measures applied there are not as effective as the same measures applied in private practice. The reason, I believe, is that patients at this hospital rarely receive an adequate diet. Recently, an attempt has been made to evaluate the effect of various vitamins on a group of senile patients; sufficient improvement has occurred in a few cases to make one believe that some symptoms are the result of dietary insufficiency. In other disorders, such as psychoneuroses and involutional melancholia, dietary insufficiency may be a factor in the production of symptoms.

A group of patients from the private practice of Dr. D. J. McCarthy were presented at a meeting of this society a short time ago by Dr. W. L. Long. It will be recalled that in this series of patients, mainly with neuroses, clinical improvement almost kept pace with gain in weight.

DR. JOSEPH C. YASKIN: The presentations and discussions this evening were so comprehensive that I had no intention of speaking. I was particularly pleased with Dr. Hadden's remarks on the need for moderation in new, or relatively new, methods of treatment, although I do not believe that psychasthenia and some other psychoneuroses can be favorably influenced by diet. I have had no experience with diet and animal experimentation. There can be no question that in some so-called neuroses, in which the primary causes are undoubtedly psychogenic, the patients show vitamin deficiency as a result of faulty diets and improve with a proper dietetic regimen, combined with large doses of vitamins and psychotherapy.

More important, perhaps, are the borderline cases of neuritis and myelitis, or perhaps myeloneuritis, occurring in middle-aged and elderly persons, often in association with alcoholism and poor dietetic regimens. These borderline conditions are frequently benefited by vitamin therapy combined with other methods. In this connection, Douthwaite (*Brit. M. J.* **2**:535 [Sept. 12] 1936) reported 7 cases in which there were marked damage to the gastric mucosa and polyneuritis. This investigator expressed the belief that the polyneuritis was due to avitaminosis related to the damage to the gastric mucosa.

DR. M. W. THORNER: There is no longer any question that under the carefully controlled conditions of the laboratory (described by Dr. Zimmerman) and

of the clinic (described by Dr. Elsom) lesions of the peripheral nerves occur. It is not correct to infer from these data that vitamin B_1 deficiency is the sole agent concerned in the production of neuritic syndromes. As Mellanby (*J. Path. & Bact.* **38**:391, 1934) has shown, vitamin A deficiency may also result in lesions of the peripheral nerves. Vitamin C deficiency has been indicted as a cause of neuritis by Hess (*J. Infect. Dis.* **23**:438, 1918) and others. Hess commented on the involvement of the nervous system in cases of vitamin D deficiency. To be sure, the evidence is not yet clear for any vitamin other than vitamin B_1. While the positive evidence is convincing, it is reasonable to maintain an open mind, so that one does not miss the woods for looking at the vitamin B_1 tree. The therapeutic implications of this attitude necessitate a diet adequate in all vitamin factors as part of the well rounded treatment for peripheral neuritis.

DR. H. M. ZIMMERMAN: The method of producing degeneration of a nerve by local injection of alcohol has been known, of course, for a long time. Animals which receive large amounts of alcohol by mouth, however, fail to show neuritis as long as their diets are adequate with respect to vitamin B. Only when this dietary factor is lacking does degeneration of peripheral nerves appear. The local effect of alcohol on a nerve is similar to that exerted by ether and is not different from that produced by nerve section.

Which chronic alcoholic patient will present clinical manifestations of pellagra and which the polyneuritis of beriberi cannot be predicted. Nor can one predict the type of anatomic changes in the nervous system. I have seen several such patients, each of whom had "axonal" changes in the ganglion cells like those associated with pellagra, pseudo-encephalitic lesions of Wernicke, degeneration of the posterior columns of the cord and demyelination of peripheral nerves. This complex anatomic picture is also sometimes observed in a patient who succumbs to a gastro-intestinal lesion, such as a carcinoma. He may even have the clinical picture of pellagra, with dermatitis, salivation, glossitis and dementia.

The question of vitamin A deficiency is interesting, but I had hoped it would not come up at this meeting, because its importance in diseases of the human nervous system is still in doubt. Lesions of the spinal cord and peripheral nerves have been shown to occur in both puppies and rats which received a diet deficient in vitamin A. The lesions were more readily produced in rats which were the offspring of mothers subsisting on a diet low in vitamin A. This type of vitamin deficiency can be complicated by B avitaminosis, since the animals lose appetite and fail to grow.

Animals with well advanced C avitaminosis have uniformly failed to show lesions of the central nervous system other than occasional petechiae. The peripheral nerves do not contain evidence of myelin destruction.

The question raised by Dr. Alpers as to the evidence for vitamin B_1 deficiency in the neuritis associated with diabetes mellitus can be answered as follows: The anatomic changes in the peripheral nerves in this condition are the same as those in beriberi. In diabetic patients who respond to insulin therapy neuritis does not develop; this complication occurs only in patients with faulty carbohydrate metabolism which cannot be controlled. The significance of this has been emphasized by Dr. Lewy. Moreover, the peripheral polyneuritis associated with diabetes mellitus has been treated successfully with vitamin B_1.

DR. F. H. LEWY: Dr. Yaskin asked why the central nervous system is involved in some animals and not in others. In concern with the deficiency in vitamins, one must not forget the general diet, i. e., the relation of fat to carbohydrate and protein. Experiments on beriberi induced in monkeys seem to indicate that use of a high protein diet in cases of B_1 avitaminosis helps to produce lesions in the central nervous system.

As to Dr. Thorner's question: I wish to emphasize a possible combination of A, B, C and D avitaminoses. While there are not yet available adequate laboratory tests for vitamin B deficiencies, there are such tests for A, C and D avitaminoses. Since an overdose of some of these vitamins is detrimental, an exact diagnosis should always precede the administration of a vitamin.

Book Reviews

Der Selbstmord. By R. Weichbrodt. Price, 19 Swiss francs. Pp. 252. Basel, Switzerland: S. Karger, 1937.

This study of suicide is in some respects comprehensive; Weichbrodt approaches the subject from many points of view, considering historical as well as sociologic and psychologic facts. The book is a typical scholastic product of a diligent worker who has collected widely distributed material, but it lacks imagination and is devoid of new ideas. It shows a remarkable knowledge of literature, but the length of the quotations is tiresome and helps little to enlighten the subject—particularly as the author is satisfied with quotations and does not give his own point of view. The quotations are from famous writers, particularly of the past—philosophers, poets and scientists—and give their personal ideas about suicide. The psychiatric approach to the problem lacks a conception of modern, dynamic psychiatry and does not consider the dynamic interplay of conflicting psychic tendencies within the personality. In spite of the fact that Weichbrodt acknowledges the importance of national and racial traditions, his statements touch no more than the surface of these traditions, as he does not see the underlying problems of group psychology.

The psychoanalytic conceptions of suicide are not discussed. Weichbrodt merely quotes a young European writer who committed suicide after writing as his motive: "I murder myself, lest I murder somebody else." He reacts to this by saying that the statement reminds one of the ideas of psychoanalysis and makes no further comment. Another example of the author's neglect of psychologic views is the fact that he gives short biographies of a number of famous persons who committed suicide, but leaves it entirely to the reader to draw conclusions. On the whole, the book contributes little to a scientific clarification of the problem of suicide.

To Drink or Not to Drink. By Charles H. Durfee, Ph.D. Price, $2. Pp. 212. New York: Longmans, Green & Co., 1937.

The central theme of this book is best expressed in the author's own words, taken from chapter 8, entitled: "A Direct Word to the Drinkers." He says: "I see your drinking only as a symptom of an underlying maladjustment. It is this maladjustment we are going to tackle, not the drink. Therefore I am not going to emphasize the drink at all, and I advise you not to try to fight it. Fighting symptoms is useless. . . . You must realize, and your family and friends also, that your drinking is not a vicious habit which you could have controlled had you really wished to. It actually stems from circumstances largely out of your control. Heredity, environment and training have made you what you are. You have not been equipped to face the realities of life. You may have ducked most of the issues that confronted you. Or, on the other hand, you may have taken them too seriously and gone beyond your endurance. Your subjective needs have warred with the objective demands of the world. Consciously or unconsciously, you have found it necessary to escape this conflict in unwholesome ways. Of these, the most socially conspicuous is alcohol."

The book is well written and could be given to patients. The case histories are brief and pointed. On the whole, however, the book contains little that is new to psychiatrists, and the ideas, though good, are too much reiterated.

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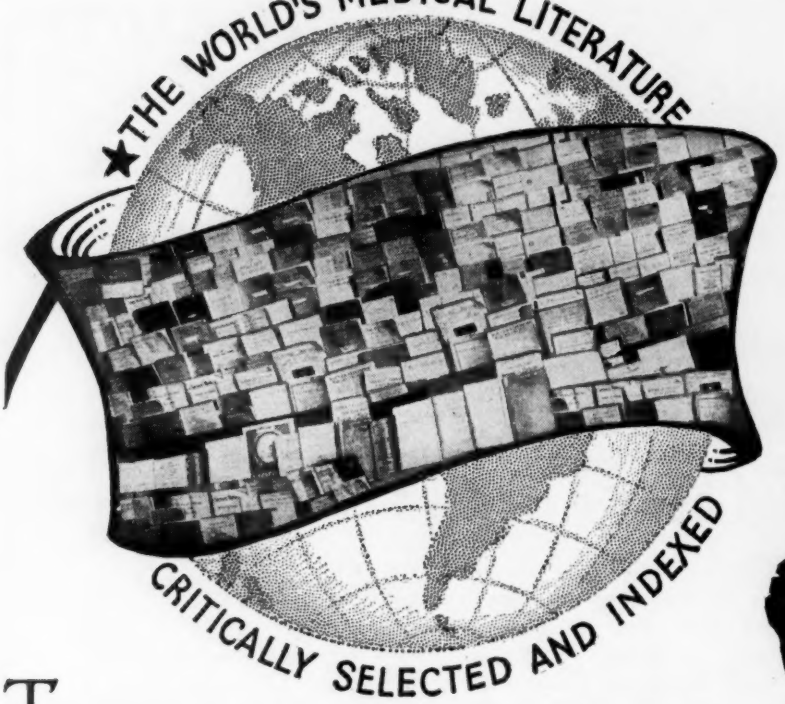

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